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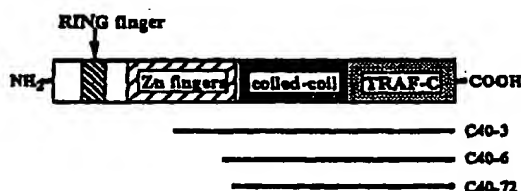
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(54) NOVEL SIGNAL TRANSDUCER

(57) TRAF5 as a novel protein and a polypeptide as a part thereof; a DNA encoding these; an antisense oligonucleotide against the DNA; an anti-TRAF5 antibody; a vector containing the DNA; a transformant prepared by using the vector; processes for producing the TRAF5 and the polypeptide as a part thereof; methods of screening substances binding to the TRAF5 or the polypeptide, substances regulating the activities of the same, and substances regulating the expression of the same by using the TRAF5 and the polypeptide; novel substances obtained by the screening; and various remedies containing these substances as the active ingredient.

Fig 1



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Description

Technical Field

5 [0001] This invention relates to a protein which associates with CD40 and transduces CD40-mediated signals, TRAF5 (Tumor Necrosis Factor Receptor-Associated Factor); polypeptides of its domains or any part thereof; DNAs encoding them; antisense oligonucleotides for the DNAs; antibodies against TRAF5 and the polypeptides of its domains; expres-
 10 sion vectors comprising said DNAs; transformants by said expression vectors; a process for the preparation of TRAF5 and the polypeptides of its domains using said transformants; a process for the screening of substances which may bind to TRAF5 and the polypeptides of its domains, or may regulate their activity or expression, using TRAF5 and the polypeptides of its domains; and medical compositions for the treatment of various diseases.

Background Art

15 [0002] After the antigen recognition, B cells will grow clonally and differentiate into antibody-producing cells under the interaction with T cells. It is considered that in the case of no association with antigen-specific T cells, B cells will terminate their growth to be inactivated or induced to apoptosis as a result of self-recognition. It has been discovered that an activity inhibiting the apoptosis exists in CD40-mediated signaling, and it has been suggested that CD40 is deeply involved in the regulation of exclusion mechanism of B cells in peripheral blood (Liu, Y.-J. et al., Nature, 342, 929, 1989,
 20 Tubata, T. et al., Nature, 364, 645, 1993). Furthermore, it has been revealed that CD40-mediated signaling may play an essential role in isotype switching of immunoglobulins, the germinal center formation and affinity maturation of antibodies (Banchereau, J., et al., Annu. Rev. Immunol., 12, 881, 1994). It is also known that the CD40-mediated signaling can induce the expression of CD23, a low-affinity IgE receptor (Cheng, G., et al., Science, 267, 1994), and that the CD40-mediated signaling is involved in the activation of a transcription factor, NFkB (Berberich, I., et al., J. Immunol., 153, 4357, 1994).

25 [0003] CD40 is expressed not only in B cells, but also in their precursors, activated macrophage/monocyte, follicular dendritic cells, Langerhans cells, thymus-epithelial cells and various cancer cells (Banchereau, J., et al., Annu. Rev. Immunol., 12, 881, 1994). It is suggested that the CD40-mediated signaling is not only essential for the activation, growth and differentiation of B cells, but also is involved in antitumor activity, the cytokines production, and the T cells
 30 activation.

[0004] CD40 has four cysteine-rich motifs in an extracellular domain and is an type-I membrane protein which belongs to NGFR family, like TNFR-1, 2 (Tumor Necrosis Factor Receptor-1, 2), Fas, OX40 and CD30.

[0005] It was reported that CD40 ligand (CD40L) was present on the activated T cells (Armitage R. J. et al., Nature, 357, 80, 1992), and has been considered that CD40-CD40L system is a crucial information-transducing mechanism in
 35 the association of B cells and T cells.

[0006] Recently, TRAF1 and TRAF2 with a TRAF (Tumor Necrosis Factor Receptor-Associated Factor) domain have been identified as a signal transducer which associates with the intracellular domain of TNFR-2. On the other hand, CD40bp, LAP-1 and CRAF1, also known as TRAF3, have been identified as a signal transducer which associates with the intracellular domain of CD40 (CD40 Receptor-Associated Factor; Cheng et al., Science, 267, 1494, 1995).

40 [0007] The present inventor has now succeeded in cloning of the gene for a novel signal transducer, mouse TRAF5 (which is the same substance as that identified as "CRAF2" in the specification of the priority application of the present application, which was filed on April 11, 1996 (the Japanese Patent Application Hei 8 (1996)-113035), by means of a two-hybrid screening using the intracellular domain protein of mouse CD40. The novel signal transducer associates with the intracellular domain of CD40, but not with that of TNFR-2. Further, cloning of the gene for human TRAF5 has
 45 been completed based on the sequence of mouse TRAF5 to lead the present invention.

Disclosure of Invention

50 [0008] The present invention relates to the novel protein TRAF5, a signal transducer which associates with the intracellular domain of CD40.

[0009] The present invention relates also to the novel protein TRAF5, a signal transducer which associates with the intracellular domain of CD40, but not with that of TNFR-2.

[0010] The present TRAF5 has no limitation with respect to its origin. The examples of the present TRAF5 are that of mouse and human, which may be characterized by an amino acid sequence of the SEQ ID No.1 or No.4 in the
 55 Sequence Listing, or their partial sequences.

[0011] It should be noted that the above amino acid sequences are only the examples of the present TRAF5, and that the present TRAF5 includes any polypeptides which have an amino acid sequence different partially from the above sequences due to deletion, substitution, addition, etc. as long as they may associate with the intracellular domain of

CD40, and which may or may not associate with that of TNFR-2. TRAF5 conjugated with sugar chains, polyethylene glycol, etc. and that fused with other proteins may also be included in the present TRAF5 as long as they possess the activity of TRAF5. The present TRAF5 is different from TRAF1, TRAF2 and CRAF1 with the TRAF domain which associates with the intracellular domain of TNFR-2 or CD40. It is considered that any substance with an amino acid sequence having a high homology to the above amino acid sequences, which has the characteristics of associating with the intracellular domain of CD40, or which has the characteristics of associating with the intracellular domain of CD40 but not with the intracellular domain of TNFR-2, may possess the function of TRAF5. Accordingly, the TRAF5 of the present invention may include the substance with an amino acid sequence having such a high homology as about 60 % or more, especially 80 % or more to the above amino acid sequences or any part thereof, that shows properties similar to mouse or human TRAF5. Human TRAF5 is preferred for use in a medical composition, as mentioned later.

[0012] The present TRAF5 is an intracellular protein, consisting of a RING finger domain, Zn finger domain, coiled-coil domain and TRAF-C domain.

[0013] The present invention therefore relates also to a polypeptide comprising at least each of the above domains or any part thereof, or to any combination of said polypeptides.

[0014] The RING finger domain, Zn finger domain, coiled-coil domain and TRAF-C domain correspond to the amino acids No. 45-84, No. 110-249, No.251-403 and No. 404-558, respectively, of the SEQ ID No.1 in the Sequence Listing, or to the amino acids No.45-84, No. 110-249, No.251-403 and No.404-557, respectively, of the SEQ ID No.4 of the Sequence Listing. These amino acid sequences, however, are the only examples of the present polypeptides. The present polypeptide includes any polypeptides which have an amino acid sequence different partially from the above ones due to deletion, substitution, addition, etc. as long as they may have the same function as any one of the above domains. Similarly, the boundaries between the domains should not be fixed to those of the above domains, and polypeptides which contain a region exceeding said boundaries in the direction of an amino- or carboxyl-terminus or both of them by further a few or ten-odd amino acids may be also included in the polypeptides of the present invention.

[0015] B cells producing an antibody against a self-antigen are usually eliminated by apoptosis, but signaling from helper T cells will rescue B cells from such apoptosis and induce them to differentiate into antibody-producing cells. The present TRAF5 and polypeptide of its part may be therefore used as a medicament to treat autoimmune disease by regulating the transduction of CD40-mediated signals.

[0016] B cells produce IgM antibody at first, but will produce IgG, IgA and IgE antibodies upon Ig isotype switching induced by CD40-mediated signaling. IgE antibody is very easily produced in allergy patients. As one of the reasons is possibly enhancement of the Ig isotype switching, the present TRAF5 and polypeptide of its part may be used as a medicament to treat allergy by regulating the transduction of CD40-mediated signals so as to inhibit the exasperation of the production of IgE.

[0017] Furthermore, since CD40-mediated signaling is involved in antitumor activity, various immune reactions such as the production of cytokines and activation of T cells, and immune diseases. The present TRAF5 and polypeptide of its part may be therefore used as a medicament with cell growth-inhibiting activity, or a medicament for the treatment of various immune diseases by regulating the transduction of CD40-mediated signals.

[0018] The present TRAF5 and polypeptide of its part may be introduced into a target cell, for example, being encapsulated in a liposome.

[0019] The present invention also relates to a DNA comprising the base sequence encoding the amino acid sequence of the present TRAF5 or its polypeptide part. The present DNAs include any type of DNA such as a genomic DNA and cDNA. The present cDNA may be prepared from mouse testis cDNA library, T cell lymphoma cDNA library, human B cell lymphoma and the like by the known methods such as colony hybridisation, plaque hybridization and PCR. The two-hybrid screening method may be used as well (Mosialos G., et al., Cell 80, 389, 1995). It is also possible to use cDNA libraries prepared from lung, thymus, spleen or kidney.

[0020] The examples of the present base sequences are illustrated as the SEQ ID No.2 and SEQ ID No.5 in the Sequence Listing. As described in the following examples, the DNAs of the SEQ ID No.3 and SEQ ID No.6 in the Sequence Listing are inserted into a plasmid vector, and *Escherichia coli* strains transformed with the vector have been deposited in the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology.

[0021] The present DNA include DNAs which comprise any other base sequences encoding the same amino acid sequence as the above, and which may be prepared by a chemical synthesis method or genetic engineering method in consideration of degeneracy of a genetic code.

[0022] Furthermore, as mentioned in the above, it is considered that the DNA encoding the polypeptide with an amino acid sequence having a high homology to TRAF5 or its polypeptide part may hybridize with the DNA of the present invention.

[0023] Accordingly, the present DNA includes DNAs which may hybridize with the base sequences shown as the SEQ ID No.2 and SEQ ID No.5 in the Sequence Listing under a stringent condition, and their DNA fragments.

[0024] The present DNA may be used for the production of TRAF5 or its polypeptide part by the genetic engineering method. It may be inserted into a suitable vector and also utilized in gene therapy. Further, transgenic animals and

knock-out animals may be prepared based on these base sequences.

[0025] Also the present invention relates to an antisense oligonucleotide and its derivatives for the present DNAs. The present antisense oligonucleotides and their derivatives may be complementarily bound to mRNA encoding the present TRAF5 or the polypeptide comprising each domain of TRAF5 or to their part so as to block their expression by inhibiting the translation of these mRNA into polypeptides.

[0026] The present antisense oligonucleotides and their derivatives include those binding to the base sequences encoding TRAF5, and those binding to non-coding regions upstream or downstream of TRAF5 as well.

[0027] The present antisense oligonucleotides and their derivatives have the base sequences complementary to the present DNA or its part. Thus, they may have a chain complementary to, for example, the DNA shown as the SEQ ID No. 2, No.3, No.5 or No.6 in the Sequence Listing or their parts. Such complementary chain may contain Uracil (U) instead of Thymine (T) as a base complementary to Adenine (A).

[0028] The present antisense oligonucleotides derivatives further include any substances which are similar to an oligonucleotide in steric structure and function, such as those in which other substances are bound to 3'- or 5'-terminus of the oligonucleotide; those in which at least one of base, sugar and phosphoric acid is replaced or modified; those containing non-naturally-occurring base, sugar or phosphoric acid; and those having a backbone other than that of sugar-phosphoric acid.

[0029] The present antisense oligonucleotides and their derivatives may be prepared by the known methods (for example, Stanley T. Crooke and Bernald Lebleu ed., in *Antisense Research and Applications*, CRC Publishing, Florida, 1993). The derivatives such as those of methyl phosphonate type or of phosphorothionate type may be prepared using a chemical synthesizer (394 type of Perkin Elmer Japan Co. Ltd., for example). In such case, the operations should be made in accordance with the instruction attached thereto and the synthesized products may be purified by a reverse HPLC chromatography method, for example, to obtain the present antisense oligonucleotides and their derivatives.

[0030] The present antisense oligonucleotides and their derivatives may be labelled with a radioisotope, fluorescent substance, enzyme or luminescent substance to use in the detection or determination of DNA or RNA encoding the present TRAF5 or its polypeptide part in a sample.

[0031] When the present antisense oligonucleotides and their derivatives are applied to medicaments, it is preferable to use those with a pharmaceutically suitable purity and in a pharmaceutically acceptable way.

[0032] The present antisense oligonucleotides and their derivatives may be used as a medicament for the treatment of allergy by regulating the transduction of CD40-mediated signals to inhibit the enhancement of the production of IgE.

[0033] The present antisense oligonucleotides and their derivatives may be used also as a medicament with cell growth-inhibiting activity, or as a medicament for the treatment of various immune diseases such as autoimmune disease by regulating the transduction of CD40-mediated signals.

[0034] The present antisense oligonucleotides and their derivatives may be used in the form of solution or suspension in a suitable solvent, or encapsulated in a liposome or inserted into a suitable vector.

[0035] Furthermore, this invention relates to an antibody recognizing the present TRAF5 or its part.

[0036] The present antibodies include ones which may cross-react with TRAF-1, TRAF-2, CRAF1 or their polypeptide parts in addition to ones which specifically recognize TRAF5 or any part thereof. There are also included antibodies recognizing only TRAF5 or any part thereof derived from a particular animal species such as human, and antibodies recognizing TRAF5 or any part thereof derived from two or more animal species.

[0037] The examples of the present antibodies are prepared using as an antigen the present TRAF5, polypeptide of each domain thereof, or fragments thereof. Thus, the DNA encoding the present TRAF5 is transformed into a suitable host cell to produce said TRAF5. The resulting TRAF5 is purified from the transformant or culture medium to use as an antigen for the production of the present antibodies in the method described later. It is also possible to synthesize chemically a polypeptide with a part of the amino acid sequence of the present TRAF5, and bind it to a carrier such as KLH (keyhole limpet hemocyanin) for use as an antigen for the production of the present antibodies in the method described later.

[0038] It is possible to prepare an antibody which recognizes TRAF5 with its whole length even using a part of the TRAF5 as an antigen. Also even if mouse TRAF5 or any part thereof is used as an antigen, an antibody which recognizes TRAF5 or any part thereof derived from human or other animal species than mouse may be prepared.

[0039] The present antibodies include monoclonal one and polyclonal one, which may be of any class or subclass. The present antibodies may be a chimera one or humanized one, or a fragment of the antibodies such as F(ab')₂ and Fab, as long as they recognize TRAF5 or any part thereof.

[0040] The present antibodies may be prepared by the known method (e.g., "Meneki jikkenho (Laboratory manual of Immunology)" published by Japan Immunological Society), as exemplified below.

[0041] The DNA encoding the present TRAF5 is transformed into a suitable host cell to produce said TRAF5. The resulting TRAF5 is purified from the transformant or culture medium. Alternatively, the polypeptide with a part of the amino acid sequence of the present TRAF5 is synthesized chemically. These resulting TRAF5 and polypeptides are conjugated with a carrier such as KLH (keyhole limpet hemocyanin) and purified to obtain an antigen. The resulting anti-

gen, alone or with a suitable adjuvant such as Freund's complete adjuvant (FCA) and Freund's incomplete adjuvant (FIA), is injected into animals at two to four-week intervals to immunize them. Blood is drawn from the immunized animals to obtain antiserum. The subject animals for immunization may be selected from rat, mouse, rabbit, sheep, horse, fowl, goat, pig, cattle and the like, depending on the type of an antibody to be desired. The polyclonal antibodies may be prepared by the purification of the resulting antiserum, using the known methods such as salting-out, ion-exchange chromatography, affinity chromatography and optional combination thereof.

[0042] Human antibodies may be prepared by in vitro sensitization method (Borrebaeck, C.A.K.J. Immunol., Meth., 123, 157, 1989), the method using SCID mouse (Toshio KUDO, Tissue Culture, 19, 61-65, 1993), etc.

[0043] The monoclonal antibodies may be prepared in the following way.

[0044] Antibody-producing cells such as spleen cells and lymphocytes are collected from the immunized animals, fused with myelomas and the like by known methods using polyethylene glycol, Sendai virus, electrical pulse to give hybridomas. Clones which produce the antibodies bonding to TRAF5 of the present invention are then selected and cultured. Monoclonal antibodies of the present invention are purified from the culture supernatant of the selected clones by known methods such as salting-out, ion-exchange chromatography, affinity chromatography and any combination thereof.

[0045] The chimera antibodies and humanized antibodies may be prepared by isolating the gene encoding the present antibodies from the hybridomas obtained above and utilizing it. For example, the chimera antibodies may be prepared by substituting a gene encoding the constant region of human antibodies for a gene encoding the constant region of the mouse antibodies, and expressing the thus reconstituted gene in animal cells. The humanized antibodies may be prepared by reconstituting a gene so that complementary determining regions (CDR) of the human antibodies are replaced with those of the mouse antibodies, and expressing the gene in animal cells (Carte et al., Proc. Nat. Acad. Sci, 89, 4285, 1992).

[0046] The present antibodies may be neutralizing antibodies, which inhibit the TRAF5 transduction of CD40-mediated signals. The neutralizing antibodies of the present invention include those that can completely inhibit the activity of TRAF5, and those partially inhibit the same.

[0047] The present antibodies may be labelled with fluorescent substances, enzymes, luminescent substances or radioisotopes to detect TRAF5 or their decomposed products present in body fluid or tissues. Since it is considered that TRAF5 is involved in transduction of CD40-mediated signals as already mentioned in the above, the detection of the existence of TRAF5 in blood or tissues would make it possible to estimate the progress of diseases and prognosis, and to confirm the effects of treatments. The present antibodies may be also used to provide an antibody-affinity column for the purification of TRAF5, or to detect TRAF5 in a fraction during the course of its purification.

[0048] The neutralizing antibodies of the present invention may serve as an effective ingredient of a medical composition for treating various diseases such as autoimmune disease by inhibiting or regulating the transduction of CD40-mediated signals.

[0049] Further, the present neutralizing antibodies may serve as an effective ingredient of a medical composition for the treatment of allergy by regulating the transduction of CD40-mediated signals to inhibit the exasperation of the production of IgE.

[0050] Also, the present invention relates to a vector comprising the DNA of the present invention. The present vector may further contain, if necessary, an enhancer sequence, promoter sequence, ribosome-binding sequence, base sequence for amplification of the number of copies, sequence encoding signal peptides, sequences encoding other polypeptides, poly(A)-additional sequence, splicing sequence, origin of replication, base sequence of the gene for selective markers and so on.

[0051] The present vector may be prepared by inserting the DNAs of the present TRAF5 or any part thereof into any vector according to the known methods (e.g., Sambrook J. et al., Molecular Cloning, a Laboratory Manual 2nd ed., Cold Spring Harbor Laboratory, New York, 1989). The preferable examples of the DNAs encoding TRAF5 or any part thereof are the base sequences shown as the SEQ ID No.2 or No.5 in the sequence Listing, or any part thereof. The present vectors include a plasmid vector, phage vector and virus vector such as pUC118, pBR322, pSV2-dhfr, pBluescriptII, pHIL-S1, λ ZapII, λ gt10, pAc700, YRP17, pEF-BOS and pEFN-II.

[0052] The preferred vectors of the present invention may optionally comprise a promoter for expression in addition to the DNAs encoding TRAF5 or any part thereof to express TRAF5 or any part thereof.

[0053] The present expression vector may be used to produce TRAF5 or any part thereof by means of genetic engineering.

[0054] The present invention therefore relates to a transformant by the above vectors. The present transformants may be prepared by transforming suitable host cells by the above vectors according to the known methods (e.g., Idenshi Kogaku Handbook (Handbook of gene technology), extra edition of Jikkenigaku, Yodo, 1991)). The host cells may be selected from procaryotic ones such as *E.coli* and *Bacillus*, or eucaryotic cells such as yeast, insect cells, and animal ones. The preferred transformants of the present invention are those derived from *E.coli*, yeast or CHO cell as a host cell to express the present TRAF5 or any part thereof.

[0055] The present invention further relates to a method for the production of TRAF5 or the present polypeptides comprising any part thereof, comprising the step of culturing the above transformants.

[0056] In the present production method, the transformants of the present invention are cultured, optionally with amplification of the gene or expression-induction, if necessary, according to the known methods (e.g. Biseibutsu Jikkenho (Laboratory manual of microbiology), Tokyo Kagaku Dojin, 1992). The culture mixture, i.e., the cells and culture supernatant, is collected and optionally subjected to concentration, solubilization, dialysis, and various chromatography such as affinity chromatography using the present antibodies to purify TRAF5 or the present polypeptides comprising any part thereof.

[0057] In the present production method, the polypeptides of the present invention may be produced by the transformants as a fusion protein with other polypeptides. In such case, the fusion protein would be treated with chemicals such as cyanogen bromide or enzymes such as protease in a certain step in the purification process, so that the polypeptides of the present invention may be excised therefrom.

[0058] The present invention also relates to a method for the screening of the substances using the present TRAF5, the polypeptides comprising any part thereof or the present antibodies against them, which substances, for example, will bind to present TRAF5 or the polypeptides, or regulate their activity or expression.

[0059] The substances binding to TRAF5 or the polypeptides comprising any part thereof, or the substances inhibiting the association between TRAF5 or the polypeptides comprising any part thereof and CD40 or the polypeptides comprising any part thereof may be screened using TRAF5 or the polypeptides comprising any part thereof, or CD40 or the polypeptides comprising any part thereof. For example, a fusion protein of TRAF5 or the polypeptides comprising any part thereof and FLAG epitope, and a fusion protein of CD40 or the polypeptides comprising any part thereof and GST are prepared according to the known method (Ishida, T. et al., Pro. Nat. Acad. Sci., 93, p.9437, 1996). These fusion proteins are then mixed with subject substances to select the substance inhibiting the association between TRAF5 or the polypeptides comprising any part thereof and CD40 or the polypeptides comprising any part thereof according to the same known method (Ishida, T. et al.).

[0060] Further, the substances inhibiting the association between TRAF5 or the polypeptides comprising any part thereof and CD40 or the polypeptides comprising any part thereof may be screened utilizing the two-hybrid method. For example, an expression vector for the expression of a fusion protein of the intracellular domain of CD40 and the DNA-binding domain of bacterial repressor LexA is prepared according to the same known method (Ishida, T. et al.). And an expression vector for the expression of a fusion protein of TRAF5 or the polypeptides comprising any part thereof and yeast protein GAL4 is prepared. These expression vectors are transformed into yeast strain L40 (Vojtek, A.B. et al., Cell, 74, p.205, 1993) to prepare a transformant according to the same known method (Ishida, T. et al.). The resulting transformant is then mixed with subject substances, followed by the detection of histidine requirement or β -galactosidase activity in order to select the substances inhibiting the association between TRAF5 or the polypeptides comprising any part thereof and CD40 or the polypeptides comprising any part thereof according to the same known method (Ishida, T. et al.).

[0061] According to the above known method (Ishida, T. et al.), substances may be screened on the basis of NF κ B activation by TRAF5. For example, an expression vector of TRAF5 and a reporter plasmid for the evaluation of NF κ B activation by TRAF5 are transformed into a human Jurkat cell or human 293T cell. The subject substances are added together and the expression of the reporter gene is detected in order to select the substance regulating the NF κ B activation by TRAF5 or the polypeptides comprising any part thereof.

[0062] Further, the substances regulating the expression of TRAF5 or the polypeptides comprising any part thereof may be screened. For example, the subject substances are added to B cells, and the expression of TRAF5 or the polypeptides comprising any part thereof is determined by using the present antibodies against the present TRAF5.

[0063] The substances binding to or regulating the activity of TRAF5 or the polypeptides comprising any part thereof may be screened using TRAF5 or the polypeptides comprising any part thereof by the following way.

[0064] Thus, TRAF5 or CD40 or the polypeptides comprising any part thereof is massively produced, purified and crystallized according to the known method (Crystallization of Nucleic Acids and Proteins, A Practical Approach, Edited by A. Ducruix and R. Giege, IRL Press at Oxford University Press, 1992).

[0065] X-ray analysis is then carried out according to the known method (Methods in Enzymology Vol.114, Diffraction Methods for Biological Macromolecules Part A, Edited by Harold W. Wyckoff, C.H.W. Hirs and Serge N. Timasheff, Academic Press, Inc. 1985) to reveal the three-dimensional structure of TRAF5 or the polypeptides comprising any part thereof, or that of their complex with CD40 or the polypeptides comprising any part thereof.

[0066] The three-dimensional structure thus revealed may be analyzed according to the known method (Methods in Enzymology Vol.115, Diffraction Methods for Biological Macromolecules Part B, Edited by Harold W. Wyckoff, C.H.W. Hirs and Serge N. Timasheff, Academic Press, Inc. 1985).

[0067] The analytical data about the above three-dimensional structure thus obtained may be used to screen or design the substances binding to TRAF5 or the polypeptides comprising any part thereof, the substances inhibiting their association with CD40 or the polypeptides comprising any part thereof, or the substances inhibiting their activity.

[0068] The present invention therefore relates to the new substances thus screened.

[0069] Such substances binding to, or regulating the activity of TRAF5 or the polypeptides comprising any part thereof may be therefore used as a medicament with cell growth-inhibiting activity, or as a medicament to treat various immune diseases such as autoimmune disease by regulating the transduction of CD40-mediated signals.

[0070] Further, the above substances may be used as a medicament to treat allergy by regulating the transduction of CD40-mediated signals to inhibit the exasperation of the production of IgE.

[0071] The effective ingredients of the present invention may be formed into their salts or be modified with pharmaceutically acceptable chemical agents, as long as they will never lose their essential activities. There may be exemplified as the salts those with inorganic acids such as hydrochloric acid, phosphoric acid, hydrobromic acid and sulfuric acid; those with organic acids such as maleic acid, succinic acid, malic acid and tartaric acid.

[0072] The medical compositions of the present invention include those administered by any route such as oral, end-ermic, intravenous, intramuscular, intraperitoneal, intracutaneous, and intrainstestinal ones.

[0073] The present medical compositions may be formulated according to the known methods depending on the administration route, and may comprise pharmaceutically acceptable auxiliaries such as excipients, filling agents, thickeners, binders, humectants, disintegrators, surfactants, solubilizers, buffers, pain-relieving agents, preservatives and stabilizers. In the case of injections, for example, they may comprise stabilizers such as gelatin, human serum albumin (HSA) and polyethylene glycol; alcohols and saccharides such as D-mannitol, D-sorbitol, and glucose; and surfactants such as Polysorbate 80 (TM).

[0074] The present medical compositions may be administered in an amount of about 0.01 ~ 100 mg/kg/day, preferably of about 0.1 ~ 10 mg/kg/day, depending on the conditions or ages of patients, or administration routes. The period for the administration is not specifically limited. It may also be continuously administered by an intravenous drip, or administered by a single dose or doses at appropriate intervals.

[0075] Summarized Description of Drawings

Fig.1 illustrates three clones associating specifically with each domain of TRAF5 and the intracellular domain of CD40.

Fig.2 shows comparison of amino acid sequences between TRAF5 and CRAF1.

Fig.3 shows the result in electrophoresis of Northern blotting of TRAF5 mRNA in various tissues.

Fig.4 shows the amino acid sequence of the intracellular domain of CD40 (from "K" at 216 to "Q" at 277) and its mutants.

Fig.5 shows the results in SDS-polyacrylamide gel electrophoresis and in electrophoresis of Western blotting of immune complex of between TRAF5 and the fusion protein consisting of GST and the intracellular domain of CD40 or its mutants.

Fig.6 shows the signal transduction activity of TRAF5 and CRAF1 using Jurkat cells and 293T cells.

Fig.7 shows the result in electrophoresis of Western blotting using the transformants of mouse WEHI-231 B cells.

Fig.8 shows the result of the inhibiting activity of induction of CD23 expression using FACS.

Fig.9 shows the result in electrophoresis of Northern blotting of human TRAF5 mRNA in the human B lymphoma cell lines, Daudi and Raji.

Fig.10 shows the signal transduction activity of TRAF5 using 293T cells.

Best Mode for carrying Out the Invention

[0076] The present invention will be illustrated by the following examples which show the best mode of the present invention. Those examples, however, should not be construed to limit the scope of the present invention by any way.

[0077] The abbreviations used in the following description are based on the conventional ones in the art.

[0078] The operations in the following examples were done mainly in accordance with Sambrook J. et al., Molecular Cloning, a Laboratory Manual 2nd ed., Cold Spring Harbor Laboratory, New York, 1989; E. Harlow, D. Lane et al., Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory; and the like.

Example 1: Preparation of DNA encoding mouse TRAF5

(1) Screening

[0079] In order to clone cDNA encoding a protein associating with the intracellular domain of mouse CD40, two-hybrid screening method was carried out. The two-hybrid screening method is a method for the detection of complex-forming activity between a two kinds of fusion proteins on the basis of activation of transcription in budding yeast cells.

[0080] A murine C57 Black Kaplan T lymphoma cell line V13 cDNA library, which had been synthesized using an expression vector pACT, was purchased from CLONTECH. The cDNA of this library could be expressed as a fusion

protein with the activation domain of yeast protein GAL4.

[0081] On the other hand, an expression vector, which may express the intracellular domain of mouse CD40 as a fusion protein with the DNA-binding domain of a bacterial repressor, LexA, was constructed in the following way.

[0082] The DNA fragment encoding the intracellular domain of mouse CD40 (Torres, R.M. et al., J. Immunol., Vol.148, 620-626, 1992: from the amino acid 216 (Lys) to the amino acid 305 (Phe)) was prepared by PCR in the following steps. At first, "5'-GCGGATCCTCAAAAAGGTGGTCAAGAAACCAAG-3'" was synthesized as a sense primer, and "5'-GCGTCGACTCAAAAAGGTCAGCAAGCAGCCATC-3'" was synthesized as an antisense primer. These primers were then mixed with cDNA of mouse WEHI-231 B cells as a template, Taq polymerase and reaction reagents (TOYOBO CO., LTD.). The reaction cycle of at 95°C for 1 min, 55°C for 2 min, and 72°C for 3 min was repeated 30 times using a DNA thermal cycler (Perkin Elmer) so as to collect an amplified product around 280 bp. After the digestion with BamHI and Sall, the product was inserted into the BamHI and Sall restriction enzyme sites of a plasmid pBTM116 (Bartel, P.L. et al., in Cellular Interactions in Development: A Practical Approach, Hartley, D.A., ed.: p.153-179, Oxford University Press, Oxford, 1993). The thus constructed plasmid was named "pBTM40cyt."

[0083] HIS3 and lacZ genes had been integrated into the genome of the yeast strain L40 (vojtek, A.B. et al., Cell, Vol.74, p.205-214, 1993). Upon the association between the LexA DNA-binding domain/the intracellular domain of CD40 fusion protein and the activation domain of GAL4/the expression product of the above cDNAs, the yeast strain L40 would be able to grow in the absence of histidine, and would be positive for the β -galactosidase activity.

[0084] The pBTM40cyt was transformed into the yeast strain L40 by the lithium acetate method to give the transformant named "L40C40" expressing the LexA DNA-binding domain/the intracellular domain of CD40 fusion protein. 2×10^6 clones of the above cDNA library were then transformed into the L40C40 by the lithium acetate method, and the resulting transformants were cultured in a histidine-free medium. After 7-day culture at 30°C, the grown clones were isolated and their β -galactosidase activity was detected in accordance with the protocol attached to the cDNA library. Seventy-two clones were selected, which showed detectable β -galactosidase activity within 20 min incubation. In order to remove cDNA clones of CRAF1 or TRAF2 which had been known to be selected by the same screening system, the selected clones were subjected to Southern blotting probed with CRAF1 or TRAF2 cDNA. Ten clones which did not hybridize with either of the two probes were used to collect the plasmids comprising the cDNA. The yeast strain L40 was cotransformed with the collected plasmids and pBTM40cyt or the vector (pBTMLamin) expressing the LexA DNA-binding domain/human lamin C fusion protein (Vojtek, A.B. et al., Cell, Vol.74, p.205-214, 1993) by the lithium acetate method. Four clones were selected, which could grow in the histidine-free medium, and showed β -galactosidase activity under the above condition only when they were cotransformed with the pBTM40cyt. Three clones (C40-3, C40-6, C40-72) of them were found to have cDNA encoding a part of the same protein (Fig.1).

[0085] The cDNA fragment of C40-3, which was the longest cDNA of the three clones, with about 1 kb was used as a probe to screen mouse testis cDNA library prepared by the known method in λ ZAPII vector (Stratagene) by the plaque hybridization method. Two independent clones were obtained, and the plasmids pBluescript having the same cDNA inserted therein were collected by in vivo excision method, followed by nucleotide sequencing with the BcaBest sequence system (Takara Shuzo). One of the two clones was revealed to comprise the longest cDNA fragment with 2105 bp (SEQ ID No. 3 in the Sequence Listing). The plasmid pBluescript into which the longest cDNA fragment had been inserted was named "pBSCRAF2 (pBSTRAF5)."

[0086] The pBSCRAF2 (pBSTRAF5) was transformed into E.coli strain NM522 by the known method, and the resulting E.coli NM522 transformant was deposited in the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology (1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken 350 Japan) on March 27, 1996 under accession numbers FERM P-15531, and then transferred on March 6, 1997 to the deposit under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and Regulation under accession numbers FERM BP-5856.

(2) Analysis of the structure of TRAF5

[0087] The analysis of the structure of TRAF5 based on the nucleotide sequence determined in the above suggested that TRAF5 was a protein consisting of 558 amino acid residues (SEQ ID No.1 in the Sequencing Listing). Homology searching against PIR data base showed its highest homology to CRAF1, as shown in Fig.2. Especially, it was revealed that a TRAF-C domain existed at the C-terminal region of TRAF5 (Fig.2). The TRAF-C domain is a motif which is known to be involved in the association with other proteins and to be present commonly in TRAF1 and TRAF2 which are known to associate with the intracellular domain of TNFR-2, and in CRAF1. It has been revealed that TRAF5 has a RING finger domain, five Zn finger domains and a coiled-coil domain in addition to the TRAF-C domain, in the order from N-terminus (Fig.1).

(3) Northern blotting

[0088] The total mRNA from various tissues was prepared by the guanidine isothiocyanate/acid-phenol method (Chomczynski, P. and Sacchi, N., *Anal. Biochem.*, Vol.162, p.156-159, 1987), and poly(A)⁺RNA was purified using oligo(dT) latex (Takara Shuzo). Seven micrograms of poly(A)⁺RNA was subjected to electrophoresis on 1% agarose gel containing 6.6% formaldehyde and transferred to a nylon membrane filter (Amersham). The nylon membrane was incubated with the probe of ³²P-labeled C40-3 cDNA fragment in hybridization buffer (0.2 M NaHPO₄ (pH 7.2), 1 mM EDTA, 1% (w/v) BSA, 7% (w/v) SDS) at 65°C. The filter was finally washed with 0.5 x SSC/0.2% (w/v) SDS at 65°C for 30 min, followed by autoradiography. The result is shown in Fig.3.

[0089] The TRAF5 mRNA was highly expressed in lung, moderately expressed in thymus, spleen and kidney, and weakly expressed in brain and liver. However, TRAF5 mRNA was not detected by Northern blotting in skeletal muscle, heart, small intestine and testis. The detection of TRAF5 mRNA with about 2.2kb confirmed that the resulting TRAF5 cDNA was a full-length copy of the corresponding mRNA.

Example 2: Determination of human CD40 region necessary for the association with TRAF5

[0090] Plasmids encoding mutants of the intracellular domain of CD40 (Stamenkovic, I. et al., *EMBO J.*, Vol.8, p.1403-1410, 1989; Fig.4) were prepared in accordance with the method of Kunkel (Kunkel, T. A., *Proc. Natl. Acad. Sci. USA*, Vol.82, p.488-492, 1985). The DNAs encoding human CD40, its mutants, or the intracellular domain of human TNFR-2 (Smith, C.A. et al., *Science*, Vol.248, p.1019-1023, 1990: from amino acid 288 (Lys) to amino acid 461 (Ser)), were subcloned into the GST fusion protein expression vector pGEX2T (Pharmacia LKB), respectively, and transformed into the *E. coli* strain BL21. The mutation sites in the intracellular domain of human CD40, which were encoded by the expression vectors, are shown in Fig. 4.

[0091] GST, GST/the intracellular domain of CD40 or its mutants fusion protein, and GST/TNFR-2 fusion protein (GST-TNFR II) were prepared in accordance with the method of Smith et al (Smith, D.B. and Johnson, K.S., *Gene*, Vol.67, p.31-40, 1988), and the resulting proteins were immobilized onto glutathione-agarose beads at a concentration of 0.2 mg/ml. Two μ l of each bead solution was subjected to electrophoresis on 12.5 % polyacrylamide/SDS gel and stained with Coomassie Brilliant Blue R-250. The results were shown in the lower part of Fig. 5.

[0092] The expression vector pME-FLAG-C40-3 was prepared by inserting the DNA encoding the protein encoded by the C40-3 cDNA and tagged with FLAG epitope (Eastman Kodak) at its amino terminus into downstream of SR α promoter of the expression vector pME18S (Bio Manual Series 4, *Gene transfection and Expression, Analytical Method*, Extra Edition of Jikkenigaku, Yodo, published April 20, 1994).

[0093] Ten micrograms of pME-FLAG-C40-3 were transfected into 10⁶ of COS7 cells. The transfected cells were harvested 36 hr after the transfection, lysed with TNE buffer (10 mM Tris-HCL (pH 7.8), 1% (W/V) NP-40, 0.15M NaCl, 10mM iodoacetamide, 1mM EDTA, 10 μ g/ml aprotinin) and centrifuged. One-half of the lysate was incubated with 1 μ g of the above proteins immobilized onto glutathione-agarose beads at 4°C for one hour. The beads were washed and boiled in the presence of 0.1% SDS followed by immune precipitation using anti-FLAG antibody M2 (Eastman Kodack). The immune complexes were subjected to electrophoresis on 12.5% polyacrylamide/SDS gel. Western blotting was then carried out using anti-FLAG antibody M2 and anti-mouse IgG antibody labeled with alkaline phosphatase by the known method. The results are shown in the upper part of Fig.5.

[0094] GST/the intracellular domain of CD40 fusion protein (GST-WT) associated well with FLAG-C40-3. The specificity of the binding (association) in this experiment was confirmed by the fact that the GST protein used as a negative control did not associate with FLAG-C40-3. On the other hand, the binding activity with FLAG-C40-3 of the mutant (GST-TA: Fig.4) was significantly reduced in comparison with GST-WT, wherein Thr-254 had been replaced by Ala. It was already known that such alternation would disable CD40 signaling linked to growth inhibition (Inui, S. et al., *Eur. J. Immunol.*, Vol.20, p.1747-1753, 1990). Among other CD40 mutants with the deletion in its intracellular domain, GST- Δ 270 (deletion of the amino acid residues 270 (Arg) - 277 (Gln) in Fig.4) showed almost the same binding activity as GST-WT, but GST- Δ 230 (deletion of the amino acid residues 230 (Lys) - 277 (Gln)) and GST- Δ 246 (deletion of the amino acid residues 246 (Asn) - 277 (Gln)) could hardly associate with FLAG-C40-3. On the other hand, compared with GST- Δ 230 and GST- Δ 246, GST- Δ 230-2A6 (deletion of the amino acid residues 230 (Asn) - 245 (Ser)) associated with FLAG-C40-3 a little. GST- Δ 239-246 (deletion of the amino acid residues 239 (Pro) - 245 (Ser)) and GST- Δ 220-239 (deletion of the amino acid residues 220 (Lys) - 238 (Phe)) also showed almost the same binding activity as GST-WT.

[0095] From the above results, it has been found that the region between 246 (Asn) and 269 (Ser) is necessary but enough for the association with TRAF5, and that either the region between 230 (Lys) and 239 (Pro) or the region between 239 (Pro) and 246 (Asn) is additionally required for the efficient association with TRAF5. Although the intracellular domain of CD40 has not yet analyzed with respect to its steric structure, it seems that TRAF5 will recognize the region ranging from 230 (Lys) to 269 (Ser) of the structure of CD40.

[0096] Incidentally, it has been reported that CRAF1 associates slightly with TNFR-2 (Mosialos, G., et al., *Cell*, Vol.80,

p.389-399, 1995). On the other hand, GST-TNFRII(TNFR-2) did not associate with FLAG-C40-3, as shown in the upper part of Fig.5, indicating that TRAF5 would not associate with TNFR-2.

Example 3: Confirmation of the signal transduction activity of TRAF5

(1) Confirmation of activation of NF κ B

[0097] Human Jurkat T cells were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum. Human 293T kidney cells were cultured in DME medium supplemented with 10% fetal bovine serum.

[0098] CRAF1 cDNA was prepared by PCR in the following steps. At first, "5'-CTCCTCGAGATGGAGTCGAG-TAAAAAGATGGAC-3'" was synthesized as a sense primer, and "5'-CTTACTAGTTCAGGGATCGGGCAGATC-CGAAGT-3'" was synthesized as an antisense primer. These primers were then mixed with cDNA of mouse spleen as a template, Taq polymerase and reaction reagents (TOYOBO CO., LTD.). The reaction cycle of at 95°C for 1 min, 55°C for 2 min, and 72°C for 3 min was repeated 30 times using a DNA thermal cycler (Perkin Elmer) so as to collect an amplified product around 1500 bp. After the digestion with XhoI and SpeI, the product was inserted into the XhoI and SpeI restriction enzyme sites of an expression vector pME18S. The thus constructed plasmid was named "pME-CRAF1." on the other hand, TRAF5 cDNA was inserted into the EcoRI and NotI restriction enzyme sites of an expression vector pME18S. The thus constructed plasmid was named "pME-TRAF5 (pME-CRAF2)."

[0099] In order to evaluate the activity of transcription factor NF- κ B, [κ B]₆TK-CAT was used as a reporter plasmid, wherein CAT would be expressed depending on a κ B site as an NF- κ B binding site (Inoue, J., et al., Proc. Natl. Acad. Sci. USA., Vol.88, p.3715-3719, 1991). Further, to confirm the κ B specificity of CAT expression, [κ BM]₆TK-CAT was used as a negative control reporter plasmid, wherein κ B site had been mutated (Inoue, J., et al., Proc. Natl. Acad. Sci. USA., Vol.88, p.3715-3719, 1991). β -actin- β -gal expressing β -galactosidase driven by β -actin promoter was also used as a reporter plasmid to evaluate the DNA transfection efficiency into cells.

[0100] The transfection of the expression vectors into Human Jurkat T cells was carried out in the following way.

[0101] One microgram of the reporter plasmid ([κ B]₆TK-CAT or [κ BM]₆TK-CAT), 1 μ g of β -actin- β -gal and 1.5 μ g or 3 μ g of pME-CRAF1 or pME-TRAF5 were mixed together, followed by the addition of pME18S to a total DNA amount of 5 μ g. The mixed DNAs were cotransfected into Jurkat T cells of 2×10^6 by the DEAE-dextran method.

[0102] The transfection of the expression vectors into Human 293T kidney cells was carried out in the following way.

[0103] One microgram of the reporter plasmid ([κ B]₆TK-CAT or [κ BM]₆TK-CAT), 1 μ g of β -actin- β -gal and 10 μ g or 20 μ g of pME-CRAF1 or pME-TRAF5 were mixed together, followed by the addition of pME18S to a total DNA amount of 22 μ g. The mixed DNAs were cotransfected into Human 293T kidney cells of 10^6 by the calcium phosphate method.

[0104] Forty-eight hours after transfection, cell extracts were prepared by collecting the cells, followed by freeze-thawing and centrifugation.

[0105] β -galactosidase activity was determined to standardize the transfection efficiency according to the method (Herbolmel, P., et al., Cell, Vol.39, p.653-662, 1984).

[0106] CAT activity was determined at 37°C for 1 hr according to the method (Gorman, C.M., et al., Mol. Cell. Biol., Vol.2, p.1044-1051, 1982). The results are shown in Fig. 6.

[0107] TRAF5 activated the κ B site-dependent transcription in human Jurkat T cells (A) in a dose-dependent manner. But CRAF1 did not show such activity. Although TRAF5 activated NF κ B activation also in human 293T kidney cells (B), but its dose-dependency was not so significant as seen in human Jurkat T cells. It was because NF κ B had been already activated to some extent without stimulation in human 293T kidney cells. This pre-activated NF κ B activity was suppressed by the overexpression of CRAF1, indicating that TRAF5 and CRAF1 showed conflicting activities with each other with respect to the activation of NF κ B by their overexpression.

(2) Confirmation of the dominant-negative mutant's inhibiting activity of the induction of CD23 expression

[0108] Mouse WEHI-231 B cells were cotransfected with pME-FLAG-C40-3 and an expression vector (pApuro) for the puromycin resistant gene (Takata, M. et al., EMBO J., Vol.13, p.1341-1349, 1994), followed by the selection in the presence of 0.5 μ g/ml of puromycin to obtain the transformants.

[0109] The expression of FLAG-C40-3 was checked for #27, #30, #41, #33, #39, #57 and their parent cell line, WEHI-231 B cells by the Western blotting method of Example 2. The clones of #33, #39 and #57 were confirmed to express FLAG-C40-3 (Fig.7). On the other hand, it was not confirmed that the clones of #27, #30, #41, and WEHI-231 B cells expressed the same protein (Fig.7). All of the transformants were confirmed to express normal levels of mouse CD40.

[0110] The above transformants were stimulated with mouse CD40L-CD8 chimeric protein (Lane, P., et al., J Exp. Med., vol.177, p.1209-1213, 1993) for 48 hr. For non-stimulating control, medium was added instead of the stimulator. The transformant cells were then stained with fluorescein isothiocyanate-conjugated anti-CD23 antibody followed by FACSscan (Becton Dickinson) analysis using the Lysis II program. The results are shown in Fig.8.

[0111] Induction of CD23 expression was scarcely observed in #33, #39 and #57, while the parent cells and #27, #30, #41 expressed CD23 after the stimulation by the CD40L-CD8 chimeric stimulator. The protein encoded by the cDNA of C40-3 lacks in the N-terminus region of TRAF5, and does not have RING finger domain and nor part of Zn finger domain, but does have TRAF-C domain (Fig.1). It was revealed that this protein acted as a dominant negative mutant for the CD40-mediated induction of CD23 expression.

Example 4: Preparation of DNA encoding human TRAF5

(1) Screening

[0112] The cDNA library of Burkitt B lymphoma cell line, Daudi (Clontech) was screened using the cDNA fragment of mouse TRAF5 obtained in Example 1 by the Plaque hybridization method. The hybridisation was carried out by incubation in the hybridisation buffer (0.2 M NaHPO₄(pH 7.2), 1mM EDTA, 1%(w/v) BSA, 7%(w/v) SDS) at 50°C. The filter was finally washed with 1 x SSC/0.1%(w/v) SDS at 50°C for 30 min, followed by autoradiography. Two independent clones were obtained, and their cDNA fragments were subcloned into a plasmid pBluescript, followed by nucleotide sequencing with the ABI PRISM cycle sequence system (Perkin Elmer). One clone was revealed to comprise the longest cDNA fragment with 3993 bp (SEQ ID No.6 in the Sequence Listing). The plasmid pBluescript into which the longest cDNA fragment had been inserted was named "pBShTRAF5."

[0113] The pBShTRAF5 was transformed into E.coli strain JM109 by the known method, and the resulting E.coli JM109 transformant was deposited in the National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology (1-3, Higashi 1-chome, Tsukubashi, Ibaraki-ken 350 Japan) on December 10, 1996 under accession numbers FERM P-15993, and then transferred on March 6, 1997 to the deposit under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and Regulation under accession numbers FERN BP-5857.

(2) Analysis of the structure of human TRAF5

[0114] The analysis of the structure of human TRAF5 based on the nucleotide sequence determined in the above (1) suggested that human TRAF5 was a protein consisting of 557 amino acid residues (SEQ ID No.4 in the Sequencing Listing). It has been revealed that human TRAF5 has 80% homology in amino acid level and 82% homology in DNA nucleotide level to mouse TRAF5. It has a RING finger domain, five Zn finger domains, a coiled-coil domain and TRAF-C domain in the order from its N-terminus.

(3) Northern blotting

[0115] Poly(A)⁺RNA of Human B lymphoma cell lines, Daudi and Raji were prepared by the same way as Example 1. Poly(A)⁺RNA (12μg) was subjected to electrophoresis on 1% agarose gel containing 6.6% formaldehyde and transferred to a nylon membrane (Amersham). Probes were prepared as follows.

[0116] At first, "5'-GCAGCAGCCGCGCCTGCAGACCGGC-3'" was synthesized as a sense primer, and "5'-ATCCAG-GAGCATTGCTGCAATATAC-3'" was synthesized as an antisense primer. These primers were then mixed with human TRAF5 cDNA as a template, Taq polymerase and reaction reagents (TOYOBO CO., LTD.). The reaction cycle of at 95°C for 1 min, 55°C for 2 min, and 72°C for 3 min was repeated 30 times using a DNA thermal cycler (Perkin Elmer) so as to collect an amplified product around 500 bp. The resulting DNA fragment was labelled with ³²P. The nylon membrane was incubated with the ³²P-labeled probe in hybridization buffer (0.2 M NaHPO₄(pH 7.2), 1mM EDTA, 1%(w/v) BSA, 7%(w/v) SDS) at 65°C. The filter was finally washed with 0.5 x SSC/0.2%(w/v) SDS at 65°C for 30 min, followed by autoradiography. The result is shown in Fig.9.

[0117] The size of the detected human TRAF5 mRNA was about 4-5 kb, confirming that the resulting human TRAF5 cDNA was almost a full-length copy of the corresponding mRNA.

Example 5: Confirmation of signal transduction activity of

(1) Confirmation of activation of NFκB

[0118] Human TRAF5's function of activating NFκB was confirmed by the same method as in Example 3. One microgram of the reporter plasmid ([κB]₆TK-CAT or [κBM]₆TK-CAT), 1 μg of β-actin-β-gal and 2, 4 or 8 μg of pME-FLAG-hTRAF5 were mixed together, followed by the addition of pME18S to a total DNA amount of 10 μg. No pME-FLAG-hTRAF5 was added to a sample used as a negative control. The mixed DNAs were cotransfected into 293T cells of 2 x 10⁶ by the calcium phosphate method. Forty eight hours after transfection, cell extracts were prepared by collecting

the cells, followed by freeze-thawing and centrifugation. CAT activity was determined. The results are shown in Fig.10.
 [0119] Human TRAF5 activated the κ B site-dependent transcription in 293T T cells in a dose-dependent manner.

SEQUENCE LISTING

SEQ ID NO : 1

Length : 558

Type : amino acid

Topology : linear

MOLECULE TYPE : peptide

ORIGINAL SOURCE

ORGANISM : mouse

SEQUENCE DESCRIPTION

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Met Ala His Ser Glu Glu Gln Ala Ala Val Pro Cys Ala Phe Ile Arg
 1          5          10          15

Gln Asn Ser Gly Asn Ser Ile Ser Leu Asp Phe Glu Pro Asp Thr Glu
          20          25          30

Tyr Gln Phe Val Glu Gln Leu Glu Glu Arg Tyr Lys Cys Ala Phe Cys
          35          40          45

His Ser Val Leu His Asn Pro His Gln Thr Gly Cys Gly His Arg Phe
          50          55          60

Cys Gln Gln Cys Ile Arg Ser Leu Arg Glu Leu Asn Ser Val Pro Ile
          65          70          75          80

Cys Pro Val Asp Lys Glu Val Ile Lys Pro Gln Glu Val Phe Lys Asp
          85          90          95

Asn Cys Cys Lys Arg Glu Val Leu Asn Leu His Val Tyr Cys Lys Asn
          100          105          110

Ala Pro Gly Cys Asn Ala Arg Ile Ile Leu Gly Arg Phe Gln Asp His
          115          120          125

Leu Gln His Cys Ser Phe Gln Ala Val Pro Cys Pro Asn Glu Ser Cys
          130          135          140

Arg Glu Ala Met Leu Arg Lys Asp Val Lys Glu His Leu Ser Ala Tyr
          145          150          155          160

Cys Arg Phe Arg Glu Glu Lys Cys Leu Tyr Cys Lys Arg Asp Ile Val
          165          170          175

Val Thr Asn Leu Gln Asp His Glu Glu Asn Ser Cys Pro Ala Tyr Pro
          180          185          190

Val Ser Cys Pro Asn Arg Cys Val Gln Thr Ile Pro Arg Ala Arg Val
          195          200          205

Asn Glu His Leu Thr Val Cys Pro Glu Ala Glu Gln Asp Cys Pro Phe
          210          215          220

Lys His Tyr Gly Cys Thr Val Lys Gly Lys Arg Gly Asn Leu Leu Glu
          225          230          235          240

His Glu Arg Ala Ala Leu Gln Asp His Met Leu Leu Val Leu Glu Lys
          245          250          255

Asn Tyr Gln Leu Glu Gln Arg Ile Ser Asp Leu Tyr Gln Ser Leu Glu
          260          265          270

Gln Lys Glu Ser Lys Ile Gln Gln Leu Ala Glu Thr Val Lys Lys Phe
          275          280          285

Glu Lys Glu Leu Lys Gln Phe Thr Gln Met Phe Gly Arg Asn Gly Thr
          290          295          300

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EP 0 915 155 A1

5 Phe Leu Ser Asn Val Gln Ala Leu Thr Ser His Thr Asp Lys Ser Ala
 305 310 315 320
 Trp Leu Glu Ala Gln Val Arg Gln Leu Leu Gln Ile Val Asn Gln Gln
 325 330 335
 Pro Ser Arg Leu Asp Leu Arg Ser Leu Val Asp Ala Val Asp Ser Val
 340 345 350
 10 Lys Gln Arg Ile Thr Gln Leu Glu Ala Ser Asp Gln Arg Leu Val Leu
 355 360 365
 Leu Glu Gly Glu Thr Ser Lys His Asp Ala His Ile Asn Ile His Lys
 370 375 380
 Ala Gln Leu Asn Lys Asn Glu Glu Arg Phe Lys Gln Leu Glu Gly Ala
 385 390 395 400
 15 Cys Tyr Ser Gly Lys Leu Ile Trp Lys Val Thr Asp Tyr Arg Val Lys
 405 410 415
 Lys Arg Glu Ala Val Glu Gly His Thr Val Ser Val Phe Ser Gln Pro
 420 425 430
 20 Phe Tyr Thr Ser Arg Cys Gly Tyr Arg Leu Cys Ala Arg Ala Tyr Leu
 435 440 445
 Asn Gly Asp Gly Ser Gly Lys Gly Thr His Leu Ser Leu Tyr Phe Val
 450 455 460
 25 Val Met Arg Gly Glu Phe Asp Ser Leu Leu Gln Trp Pro Phe Arg Gln
 465 470 475 480
 Arg Val Thr Leu Met Leu Leu Asp Gln Ser Gly Lys Lys Asn His Ile
 485 490 495
 Val Glu Thr Phe Lys Ala Asp Pro Asn Ser Ser Ser Phe Lys Arg Pro
 500 505 510
 30 Asp Gly Glu Met Asn Ile Ala Ser Gly Cys Pro Arg Phe Val Ser His
 515 520 525
 Ser Thr Leu Glu Asn Ser Lys Asn Thr Tyr Ile Lys Asp Asp Thr Leu
 530 535 540
 35 Phe Leu Lys Val Ala Val Asp Leu Thr Asp Leu Glu Asp Leu
 545 550 555

SEQ ID NO : 2
 LENGTH : 1674
 TYPE : nucleic acid
 STRANDNESS : double
 TOPOLOGY : linear
 MOLECULE TYPE : cDNA to mRNA
 ORIGINAL SOURCE
 ORGANISM : mouse
 FEATURE
 Feature Key : CDS
 Location : 1..1674
 Method for the determination of feature : P
 SEQUENCE DESCRIPTION

48
 ATG GCT CAT TCG GAG GAG CAA GCG GCT GTC CCC TGC GCC TTC ATC CGC
 Met Ala His Ser Glu Glu Gln Ala Ala Val Pro Cys Ala Phe Ile Arg
 1 5 10 15

EP 0 915 155 A1

	CAG AAC TCT GGC AAC TCA ATT TCC TTG GAC TTT GAG CCC GAC ACC GAG Gln Asn Ser Gly Asn Ser Ile Ser Leu Asp Phe Glu Pro Asp Thr Glu	96
5	TAC CAG TTT GTG GAG CAG CTG GAA GAA CGC TAC AAA TGT GCC TTC TGC Tyr Gln Phe Val Glu Gln Leu Glu Glu Arg Tyr Lys Cys Ala Phe Cys	144
10	CAC TCC GTG CTT CAC AAC CCC CAC CAG ACC GGC TGC GGG CAC CGC TTC His Ser Val Leu His Asn Pro His Gln Thr Gly Cys Gly His Arg Phe	192
15	TGC CAG CAG TGC ATC CGG TCT CTG AGA GAA TTG AAC TCG GTG CCG ATC Cys Gln Gln Cys Ile Arg Ser Leu Arg Glu Leu Asn Ser Val Pro Ile	240
20	TGC CCG GTA GAC AAG GAG GTC ATC AAG CCT CAG GAG GTG TTC AAA GAC Cys Pro Val Asp Lys Glu Val Ile Lys Pro Gln Glu Val Phe Lys Asp	288
25	AAC TGC TGC AAA AGA GAA GTT CTC AAT TTA CAC GTC TAC TGC AAA AAC Asn Cys Cys Lys Arg Glu Val Leu Asn Leu His Val Tyr Cys Lys Asn	336
30	GCC CCC GGG TGC AAT GCC AGG ATT ATT CTG GGA CGA TTC CAG GAC CAC Ala Pro Gly Cys Asn Ala Arg Ile Ile Leu Gly Arg Phe Gln Asp His	384
35	CTT CAG CAC TGT TCC TTC CAA GCC GTG CCC TGC CCT AAC GAG AGC TGC Leu Gln His Cys Ser Phe Gln Ala Val Pro Cys Pro Asn Glu Ser Cys	432
40	CGG GAA GCC ATG CTC CGG AAA GAC GTG AAA GAG CAC CTG AGC GCA TAC Arg Glu Ala Met Leu Arg Lys Asp Val Lys Glu His Leu Ser Ala Tyr	480
45	TGC CCG TTC CGA GAG GAG AAG TGC CTT TAC TGC AAA AGG GAC ATA GTG Cys Arg Phe Arg Glu Lys Cys Leu Tyr Cys Lys Arg Asp Ile Val	528
50	GTG ACC AAC CTG CAG GAT CAT GAG GAA AAC TCG TGT CCT GCG TAC CCA Val Thr Asn Leu Gln Asp His Glu Glu Asn Ser Cys Pro Ala Tyr Pro	576
55	GTG TCT TGT CCC AAC AGG TGT GTG CAG ACT ATT CCA AGA GCT AGG GTG Val Ser Cys Pro Asn Arg Cys Val Gln Thr Ile Pro Arg Ala Arg Val	624
60	AAT GAA CAC CTT ACT GTA TGT CCT GAG GCT GAG CAA GAC TGT CCC TTT Asn Glu His Leu Thr Val Cys Pro Glu Ala Glu Gln Asp Cys Pro Phe	672
65	AAG CAC TAT GGC TGC ACT GTC AAG GGT AAG CGG GGG AAC TTG CTG GAG Lys His Tyr Gly Cys Thr Val Lys Gly Lys Arg Gly Asn Leu Leu Glu	720
70	CAT GAG CCG GCA GCC CTG CAG GAC CAC ATG CTT CTG GTT TTA GAG AAG His Glu Arg Ala Ala Leu Gln Asp His Met Leu Leu Val Leu Glu Lys	768
75	AAC TAC CAA CTA GAA CAG CGG ATC TCT GAT TTA TAT CAG AGT CTC GAA Asn Tyr Gln Leu Glu Gln Arg Ile Ser Asp Leu Tyr Gln Ser Leu Glu	816
80	CAG AAG GAA AGC AAG ATC CAG CAG CTG GCA GAA ACC GTG AAG AAG TTC Gln Lys Glu Ser Lys Ile Gln Gln Leu Ala Glu Thr Val Lys Lys Phe	864

	GAA AAG GAG CTT AAG CAG TTC ACA CAG ATG TTT GGC AGA AAT GGA ACT	912
	Glu Lys Glu Leu Lys Gln Phe Thr Gln Met Phe Gly Arg Asn Gly Thr	
5	290 295 300	
	TTC CTC TCA AAT GTC CAG GCT CTC ACC AGT CAC ACG GAC AAG TCA GCT	960
	Phe Leu Ser Asn Val Gln Ala Leu Thr Ser His Thr Asp Lys Ser Ala	
	305 310 315 320	
	TGG CTG GAA GCG CAG GTG CGG CAG CTG CTA CAA ATA GTT AAC CAG CAG	1008
10	Trp Leu Glu Ala Gln Val Arg Gln Leu Leu Gln Ile Val Asn Gln Gln	
	325 330 335	
	CCA AGT CGA CTT GAT CTG AGG TCT TTG GTG GAT GCG GTT GAC AGC GTG	1056
	Pro Ser Arg Leu Asp Leu Arg Ser Leu Val Asp Ala Val Asp Ser Val	
	340 345 350	
	AAA CAG AGG ATC ACC CAG CTG GAA GCC AGT GAC CAG AGA TTA GTT CTT	1104
15	Lys Gln Arg Ile Thr Gln Leu Glu Ala Ser Asp Gln Arg Leu Val Leu	
	355 360 365	
	TTA GAG GGG GAG ACC AGC AAG CAC GAC GCA CAC ATT AAT ATC CAC AAA	1152
	Leu Glu Gly Glu Thr Ser Lys His Asp Ala His Ile Asn Ile His Lys	
	370 375 380	
	GCA CAG CTG AAT AAG AAC GAA GAG CGG TTT AAG CAG CTG GAG GGC GCC	1200
20	Ala Gln Leu Asn Lys Asn Glu Glu Arg Phe Lys Gln Leu Glu Gly Ala	
	385 390 395 400	
	TGC TAC AGT GGC AAG CTC ATC TGG AAG GTG ACA GAT TAC AGG GTG AAG	1248
	Cys Tyr Ser Gly Lys Leu Ile Trp Lys Val Thr Asp Tyr Arg Val Lys	
	405 410 415	
	AAG AGG GAG GCC GTG GAG GGG CAC ACA GTG TCC GTC TTC AGC CAG CCT	1296
25	Lys Arg Glu Ala Val Glu Gly His Thr Val Ser Val Phe Ser Gln Pro	
	420 425 430	
	TTC TAC ACC AGC CGC TGC GGC TAC CGG CTC TGT GCC AGG GCG TAC CTG	1344
	Phe Tyr Thr Ser Arg Cys Gly Tyr Arg Leu Cys Ala Arg Ala Tyr Leu	
	435 440 445	
30	AAC GGG GAC GGG TCG GGG AAG GGA ACG CAC CTG TCC CTG TAC TTT GTG	1392
	Asn Gly Asp Gly Ser Gly Lys Gly Thr His Leu Ser Leu Tyr Phe Val	
	450 455 460	
	GTG ATG CGC GGT GAG TTT GAC TCG CTG CTG CAG TGG CCG TTC AGG CAG	1440
35	Val Met Arg Gly Glu Phe Asp Ser Leu Leu Gln Trp Pro Phe Arg Gln	
	465 470 475 480	
	AGG GTG ACC CTG ATG CTT TTG GAC CAG AGC GGC AAG AAG AAC CAT ATT	1488
	Arg Val Thr Leu Met Leu Leu Asp Gln Ser Gly Lys Lys Asn His Ile	
	485 490 495	
	GTG GAG ACC TTC AAA GCT GAC CCC AAC AGC AGC AGC TTC AAA AGG CCA	1536
40	Val Glu Thr Phe Lys Ala Asp Pro Asn Ser Ser Ser Phe Lys Arg Pro	
	500 505 510	
	GAT GGC GAG ATG AAC ATT GCC TCT GGC TGT CCC CGC TTT GTG TCG CAC	1584
	Asp Gly Glu Met Asn Ile Ala Ser Gly Cys Pro Arg Phe Val Ser His	
	515 520 525	
	TCT ACT CTG GAG AAC TCC AAG AAC ACC TAC ATT AAA GAC GAC ACA CTG	1632
45	Ser Thr Leu Glu Asn Ser Lys Asn Thr Tyr Ile Lys Asp Asp Thr Leu	
	530 535 540	
	TTC TTG AAA GTG GCC GTG GAT TTA ACT GAC TTG GAG GAT CTG	1674
	Phe Leu Lys Val Ala Val Asp Leu Thr Asp Leu Glu Asp Leu	
50		
55		

545

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555

SEQ ID NO : 3
 LENGTH : 2105
 TYPE : nucleic acid
 STRANDNESS : double
 TOPOLOGY : linear
 MOLECULE TYPE : cDNA to mRNA
 ORIGINAL SOURCE
 ORGANISM : mouse
 IMMEDIATE SOURCE
 CLONE : pBSCRAF2 (pBSTRAF5)
 FEATURE
 Feature Key : CDS
 Location : 188..1861
 Method for the determination of feature : P
 SEQUENCE DESCRIPTION

TGTGAGCCGG AGGCGTGTGT GGTAGCGGGC GAACTGAGGC GACGCGGGAC ACCCGCGCCC 60
 GGCCGAGGGC ACTTTTGCAA GACTTGTGAG CACAGCCCGT TAACGTGAGC TTAATGCCAG 120
 GGTCTCGAGC CTGCGCCGGT GCTATAGCGC GTGCTCGATT GGAAACAGAA CCGACTCTG 180
 CAGAAGA ATG GCT CAT TCG GAG GAG CAA GCG GCT GTC CCC TGC GCC TTC 229
 Met Ala His Ser Glu Glu Gln Ala Ala Val Pro Cys Ala Phe
 1 5 10
 ATC CGC CAG AAC TCT GGC AAC TCA ATT TCC TTG GAC TTT GAG CCC GAC 277
 Ile Arg Gln Asn Ser Gly Asn Ser Ile Ser Leu Asp Phe Glu Pro Asp
 15 20 25 30
 ACC GAG TAC CAG TTT GTG GAG CAG CTG GAA GAA CGC TAC AAA TGT GCC 325
 Thr Glu Tyr Gln Phe Val Glu Gln Leu Glu Glu Arg Tyr Lys Cys Ala
 35 40 45
 TTC TGC CAC TCC GTG CTT CAC AAC CCC CAC CAG ACC GGC TGC GGG CAC 373
 Phe Cys His Ser Val Leu His Asn Pro His Gln Thr Gly Cys Gly His
 50 55 60
 CGC TTC TGC CAG CAG TGC ATC CGG TCT CTG AGA GAA TTG AAC TCG GTG 421
 Arg Phe Cys Gln Gln Cys Ile Arg Ser Leu Arg Glu Leu Asn Ser Val
 65 70 75
 CCG ATC TGC CCG GTA GAC AAG GAG GTC ATC AAG CCT CAG GAG GTG TTC 469
 Pro Ile Cys Pro Val Asp Lys Glu Val Ile Lys Pro Gln Glu Val Phe
 80 85 90
 AAA GAC AAC TGC TGC AAA AGA GAA GTT CTC AAT TTA CAC GTC TAC TGC 517
 Lys Asp Asn Cys Cys Lys Arg Glu Val Leu Asn Leu His Val Tyr Cys
 95 100 105 110
 AAA AAC GCC CCC GGG TGC AAT GCC AGG ATT ATT CTG GGA CGA TTC CAG 565
 Lys Asn Ala Pro Gly Cys Asn Ala Arg Ile Ile Leu Gly Arg Phe Gln
 115 120 125
 GAC CAC CTT CAG CAC TGT TCC TTC CAA GCC GTG CCC TGC CCT AAC GAG 613
 Asp His Leu Gln His Cys Ser Phe Gln Ala Val Pro Cys Pro Asn Glu
 130 135 140
 AGC TGC CGG GAA GCC ATG CTC CGG AAA GAC GTG AAA GAG CAC CTG AGC 661
 Ser Cys Arg Glu Ala Met Leu Arg Lys Asp Val Lys Glu His Leu Ser
 145 150 155
 GCA TAC TGC CGG TTC CGA GAG GAG AAG TGC CTT TAC TGC AAA AGG GAC 709
 Ala Tyr Cys Arg Phe Arg Glu Glu Lys Cys Leu Tyr Cys Lys Arg Asp

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	160	165	170	
5	ATA GTG GTG ACC AAC CTG CAG GAT CAT GAG GAA AAC TCG TGT CCT GCG Ile Val Val Thr Asn Leu Gln Asp His Glu Glu Asn Ser Cys Pro Ala 175 180 185 190	757		
	TAC CCA GTG TCT TGT CCC AAC AGG TGT GTG CAG ACT ATT CCA AGA GCT Tyr Pro Val Ser Cys Pro Asn Arg Cys Val Gln Thr Ile Pro Arg Ala 195 200 205	805		
10	AGG GTG AAT GAA CAC CTT ACT GTA TGT CCT GAG GCT GAG CAA GAC TGT Arg Val Asn Glu His Leu Thr Val Cys Pro Glu Ala Glu Gln Asp Cys 210 215 220	853		
	CCC TTT AAG CAC TAT GGC TGC ACT GTC AAG GGT AAG CGG GCG AAC TTG Pro Phe Lys His Tyr Gly Cys Thr Val Lys Gly Lys Arg Gly Asn Leu 225 230 235	901		
15	CTG GAG CAT GAG CGG GCA GCC CTG CAG GAC CAC ATG CTT CTG GTT TTA Leu Glu His Glu Arg Ala Ala Leu Gln Asp His Met Leu Leu Val Leu 240 245 250	949		
	GAG AAG AAC TAC CAA CTA GAA CAG CGG ATC TCT GAT TTA TAT CAG AGT Glu Lys Asn Tyr Gln Leu Glu Gln Arg Ile Ser Asp Leu Tyr Gln Ser 255 260 265 270	997		
20	CTC GAA CAG AAG GAA AGC AAG ATC CAG CAG CTG GCA GAA ACC GTG AAG Leu Glu Gln Lys Glu Ser Lys Ile Gln Gln Leu Ala Glu Thr Val Lys 275 280 285	1045		
	AAG TTC GAA AAG GAG CTT AAG CAG TTC ACA CAG ATG TTT GGC AGA AAT Lys Phe Glu Lys Glu Leu Lys Gln Phe Thr Gln Met Phe Gly Arg Asn 290 295 300	1093		
25	GGA ACT TTC CTC TCA AAT GTC CAG GCT CTC ACC AGT CAC ACG GAC AAG Gly Thr Phe Leu Ser Asn Val Gln Ala Leu Thr Ser His Thr Asp Lys 305 310 315	1141		
	TCA GCT TGG CTG GAA GCG CAG GTG CGG CAG CTG CTA CAA ATA GTT AAC Ser Ala Trp Leu Glu Ala Gln Val Arg Gln Leu Leu Gln Ile Val Asn 320 325 330	1189		
30	CAG CAG CCA AGT CGA CTT GAT CTG AGG TCT TTG GTG GAT GCG GTT GAC Gln Gln Pro Ser Arg Leu Asp Leu Arg Ser Leu Val Asp Ala Val Asp 335 340 345 350	1237		
	AGC GTG AAA CAG AGG ATC ACC CAG CTG GAA GCC AGT GAC CAG AGA TTA Ser Val Lys Gln Arg Ile Thr Gln Leu Glu Ala Ser Asp Gln Arg Leu 355 360 365	1285		
35	GTT CTT TTA GAG GGG GAG ACC AGC AAG CAC GAC GCA CAC ATT AAT ATC Val Leu Leu Glu Gly Glu Thr Ser Lys His Asp Ala His Ile Asn Ile 370 375 380	1333		
40	CAC AAA GCA CAG CTG AAT AAG AAC GAA GAG CGG TTT AAG CAG CTG GAG His Lys Ala Gln Leu Asn Lys Asn Glu Glu Arg Phe Lys Gln Leu Glu 385 390 395	1381		
	GGC GCC TGC TAC AGT GGC AAG CTC ATC TGG AAG GTG ACA GAT TAC AGG Gly Ala Cys Tyr Ser Gly Lys Leu Ile Trp Lys Val Thr Asp Tyr Arg 400 405 410	1429		
45	GTG AAG AAG AGG GAG GCC GTG GAG GGG CAC ACA GTG TCC GTC TTC AGC Val Lys Lys Arg Glu Ala Val Glu Gly His Thr Val Ser Val Phe Ser 415 420 425 430	1477		
50	CAG CCT TTC TAC ACC AGC CGC TGC GGC TAC CGG CTC TGT GCC AGG GCG	1525		

5 Gln Pro Phe Tyr Thr Ser Arg Cys Gly Tyr Arg Leu Cys Ala Arg Ala
 435 440 445
 TAC CTG AAC GGG GAC GGG TCG GGG AAG GGA ACG CAC CTG TCC CTG TAC 1573
 Tyr Leu Asn Gly Asp Gly Ser Gly Lys Gly Thr His Leu Ser Leu Tyr
 450 455 460
 10 TTT GTG GTG ATG CGC GGT GAG TTT GAC TCG CTG CTG CAG TGG CCG TTC 1621
 Phe Val Val Met Arg Gly Glu Phe Asp Ser Leu Leu Gln Trp Pro Phe
 465 470 475
 AGG CAG AGG GTG ACC CTG ATG CTT TTG GAC CAG AGC GGC AAG AAG AAC 1669
 Arg Gln Arg Val Thr Leu Met Leu Leu Asp Gln Ser Gly Lys Lys Asn
 480 485 490
 15 CAT ATT GTG GAG ACC TTC AAA GCT GAC CCC AAC AGC AGC AGC TTC AAA 1717
 His Ile Val Glu Thr Phe Lys Ala Asp Pro Asn Ser Ser Ser Phe Lys
 495 500 505
 AGG CCA GAT GGC GAG ATG AAC ATT GCC TCT GGC TGT CCC CGC TTT GTG 1765
 Arg Pro Asp Gly Glu Met Asn Ile Ala Ser Gly Cys Pro Arg Phe Val
 515 520 525
 20 TCG CAC TCT ACT CTG GAG AAC TCC AAG AAC ACC TAC ATT AAA GAC GAC 1813
 Ser His Ser Thr Leu Glu Asn Ser Lys Asn Thr Tyr Ile Lys Asp Asp
 530 535 540
 ACA CTG TTC TTG AAA GTG GCC GTG GAT TTA ACT GAC TTG GAG GAT CTG 1861
 Thr Leu Phe Leu Lys Val Ala Val Asp Leu Thr Asp Leu Glu Asp Leu
 545 550 555
 25 TAGTGTACC TGATAAGGAA ACTTCTCAGC ACAGGAAAAG GTGTGGCTGT CCCTTGGGCG 1921
 CAGCCCTCTG GACTGAGCAG GCTCTTGTTT TTGTCTTCCT GCCTCCGATG TCTGATGTGT 1981
 CATCTTTTAA TCTTGGATCC TTCCCTGGTT TGAACCTTTA AACTCTTGAA ATATTGCTGT 2041
 30 TATTTATATT TTTGTATCTT CCAAAAAATT ATAATAATTT GACAACAAAA AAAAAAAAAA 2101
 AAAA 2105
 SEQ ID NO : 4
 LENGTH : 557
 TYPE : amino acid
 TOPOLOGY : linear
 MOLECULE TYPE : peptide
 ORIGINAL SOURCE
 ORGANISM : human
 SEQUENCE DESCRIPTION
 35 Met Ala Tyr Ser Glu Glu His Lys Gly Met Pro Cys Gly Phe Ile Arg
 1 5 10 15
 Gln Asn Ser Gly Asn Ser Ile Ser Leu Asp Phe Glu Pro Ser Ile Glu
 20 25 30
 40 Tyr Gln Phe Val Glu Arg Leu Glu Glu Arg Tyr Lys Cys Ala Phe Cys
 35 40 45
 His Ser Val Leu His Asn Pro His Gln Thr Gly Cys Gly His Arg Phe
 50 55 60
 50 Cys Gln His Cys Ile Leu Ser Leu Arg Glu Leu Asn Thr Val Pro Ile
 65 70 75 80

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Cys Pro Val Asp Lys Glu Val Ile Lys Ser Gln Glu Val Phe Lys Asp
 85 90 95
 5 Asn Cys Cys Lys Arg Glu Val Leu Asn Leu Tyr Val Tyr Cys Ser Asn
 100 105 110
 Ala Pro Gly Cys Asn Ala Lys Val Ile Leu Gly Arg Tyr Gln Asp His
 115 120 125
 10 Leu Gln Gln Cys Leu Phe Gln Pro Val Gln Cys Ser Asn Glu Lys Cys
 130 135 140
 Arg Glu Pro Val Leu Arg Lys Asp Leu Lys Glu His Leu Ser Ala Ser
 145 150 155 160
 Cys Gln Phe Arg Lys Glu Lys Cys Leu Tyr Cys Lys Lys Asp Val Val
 165 170 175
 15 Val Ile Asn Leu Gln Asn His Glu Glu Asn Leu Cys Pro Glu Tyr Pro
 180 185 190
 Val Phe Cys Pro Asn Asn Cys Ala Lys Ile Ile Leu Lys Thr Glu Val
 195 200 205
 20 Asp Glu His Leu Ala Val Cys Pro Glu Ala Glu Gln Asp Cys Pro Phe
 210 215 220
 Lys His Tyr Gly Cys Ala Val Thr Asp Lys Arg Arg Asn Leu Gln Gln
 225 230 235 240
 25 His Glu His Ser Ala Leu Arg Glu His Met Arg Leu Val Leu Glu Lys
 245 250 255
 Asn Val Gln Leu Glu Glu Gln Ile Ser Asp Leu His Lys Ser Leu Glu
 260 265 270
 Gln Lys Glu Ser Lys Ile Gln Gln Leu Ala Glu Thr Ile Lys Lys Leu
 275 280 285
 30 Glu Lys Glu Phe Lys Gln Phe Ala Gln Leu Phe Gly Lys Asn Gly Ser
 290 295 300
 Phe Leu Pro Asn Ile Gln Val Phe Ala Ser His Ile Asp Lys Ser Ala
 305 310 315 320
 35 Trp Leu Glu Ala Gln Val His Gln Leu Leu Gln Met Val Asn Gln Gln
 325 330 335
 Gln Asn Lys Phe Asp Leu Arg Pro Leu Met Glu Ala Val Asp Thr Val
 340 345 350
 40 Lys Gln Lys Ile Thr Leu Leu Glu Asn Asn Asp Gln Arg Leu Ala Val
 355 360 365
 Leu Glu Glu Glu Thr Asn Lys His Asp Thr His Ile Asn Ile His Lys
 370 375 380
 Ala Gln Leu Ser Lys Asn Glu Glu Arg Phe Lys Leu Leu Glu Gly Thr
 385 390 395 400
 45 Cys Tyr Asn Gly Lys Leu Ile Trp Lys Val Thr Asp Tyr Lys Met Lys
 405 410 415
 Lys Arg Glu Ala Val Asp Gly His Thr Val Ser Ile Phe Ser Gln Ser
 420 425 430
 50 Phe Tyr Thr Ser Arg Cys Gly Tyr Arg Leu Cys Ala Arg Ala Tyr Leu

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435 440 445
 Asn Gly Asp Gly Ser Gly Arg Gly Ser His Leu Ser Leu Tyr Phe Val
 450 455 460
 Val Met Arg Gly Glu Phe Asp Ser Leu Leu Gln Trp Pro Phe Arg Gln
 465 470 475 480
 Arg Val Thr Leu Met Leu Leu Asp Gln Ser Gly Lys Lys Asn Ile Met
 485 490 495
 Glu Thr Phe Lys Pro Asp Pro Asn Ser Ser Ser Phe Lys Arg Pro Asp
 500 505 510
 Gly Glu Met Asn Ile Ala Ser Gly Cys Pro Arg Phe Val Ala His Ser
 515 520 525
 Val Leu Glu Asn Ala Lys Asn Ala Tyr Ile Lys Asp Asp Thr Leu Phe
 530 535 540
 Leu Lys Val Ala Val Asp Leu Thr Asp Leu Glu Asp Leu
 545 550 555

 SEQ ID NO : 5
 LENGTH : 1671
 TYPE : nucleic acid
 STRANDNESS : double
 TOPOLOGY : linear
 MOLECULE TYPE : cDNA to mRNA
 ORIGINAL SOURCE
 ORGANISM : human
 FEATURE
 Feature Key : CDS
 Location : 1..1671
 Method for the determination of feature : P
 SEQUENCE DESCRIPTION

 ATG GCT TAT TCA GAA GAG CAT AAA GGT ATG CCC TGT GGT TTC ATC CGC 48
 Met Ala Tyr Ser Glu Glu His Lys Gly Met Pro Cys Gly Phe Ile Arg
 1 5 10 15
 CAG AAT TCC GGC AAC TCC ATT TCC TTG GAC TTT GAG CCC AGT ATA GAG 96
 Gln Asn Ser Gly Asn Ser Ile Ser Leu Asp Phe Glu Pro Ser Ile Glu
 20 25 30
 TAC CAG TTT GTG GAG CGG TTG GAA GAG CGC TAC AAA TGT GCC TTC TGC 144
 Tyr Gln Phe Val Glu Arg Leu Glu Glu Arg Tyr Lys Cys Ala Phe Cys
 35 40 45
 CAC TCG GTG CTT CAC AAC CCC CAC CAG ACA GGA TGT GGG CAC CGC TTC 192
 His Ser Val Leu His Asn Pro His Gln Thr Gly Cys Gly His Arg Phe
 50 55 60
 TGC CAG CAC TGC ATC CTG TCC CTG AGA GAA TTA AAC ACA GTG CCA ATC 240
 Cys Gln His Cys Ile Leu Ser Leu Arg Glu Leu Asn Thr Val Pro Ile
 65 70 75 80
 TGC CCT GTA GAT AAA GAG GTC ATC AAA TCT CAG GAG GTT TTT AAA GAC 288
 Cys Pro Val Asp Lys Glu Val Ile Lys Ser Gln Glu Val Phe Lys Asp
 85 90 95
 AAT TGT TGC AAA AGA GAA GTC CTC AAC TTA TAT GTA TAT TGC AGC AAT 336
 Asn Cys Cys Lys Arg Glu Val Leu Asn Leu Tyr Val Tyr Cys Ser Asn
 100 105 110
 GCT CCT GGA TGT AAT GCC AAG GTT ATT CTG GGC CGG TAC CAG GAT CAC 384
 50

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	Ala	Pro	Gly	Cys	Asn	Ala	Lys	Val	Ile	Leu	Gly	Arg	Tyr	Gln	Asp	His	
			115					120					125				
5	CTT	CAG	CAG	TGC	TTA	TTT	CAA	CCT	GTG	CAG	TGT	TCT	AAT	GAG	AAG	TGC	432
	Leu	Gln	Gln	Cys	Leu	Phe	Gln	Pro	Val	Gln	Cys	Ser	Asn	Glu	Lys	Cys	
			130				135					140					
	CGG	GAG	CCA	GTC	CTA	CGG	AAA	GAC	CTG	AAA	GAG	CAT	TTG	AGT	GCA	TCC	480
	Arg	Glu	Pro	Val	Leu	Arg	Lys	Asp	Leu	Lys	Glu	His	Leu	Ser	Ala	Ser	
			145			150					155				160		
10	TGT	CAG	TTT	CGA	AAG	GAA	AAA	TGC	CTT	TAT	TGC	AAA	AAG	GAT	GTG	GTA	528
	Cys	Gln	Phe	Arg	Lys	Glu	Lys	Cys	Leu	Tyr	Cys	Lys	Lys	Asp	Val	Val	
					165					170					175		
	GTC	ATC	AAT	CTA	CAG	AAT	CAT	GAG	GAA	AAC	TTG	TGT	CCT	GAA	TAC	CCA	576
	Val	Ile	Asn	Leu	Gln	Asn	His	Glu	Glu	Asn	Leu	Cys	Pro	Glu	Tyr	Pro	
15				180					185					190			
	GTA	TTT	TGT	CCC	AAC	AAT	TGT	GCG	AAG	ATT	ATT	CTA	AAA	ACT	GAG	GTA	624
	Val	Phe	Cys	Pro	Asn	Asn	Cys	Ala	Lys	Ile	Ile	Leu	Lys	Thr	Glu	Val	
			195				200						205				
	GAT	GAA	CAC	CTG	GCT	GTA	TGT	CCT	GAA	GCT	GAG	CAA	GAC	TGT	CCT	TTT	672
20	Asp	Glu	His	Leu	Ala	Val	Cys	Pro	Glu	Ala	Glu	Gln	Asp	Cys	Pro	Phe	
		210					215					220					
	AAG	CAC	TAT	GGC	TGT	GCT	GTA	ACG	GAT	AAA	CGG	AGG	AAC	CTG	CAG	CAA	720
	Lys	His	Tyr	Gly	Cys	Ala	Val	Thr	Asp	Lys	Arg	Arg	Asn	Leu	Gln	Gln	
		225				230					235				240		
25	CAT	GAG	CAT	TCA	GCC	TTA	CGG	GAG	CAC	ATG	CGT	TTG	GTT	TTA	GAA	AAG	768
	His	Glu	His	Ser	Ala	Leu	Arg	Glu	His	Met	Arg	Leu	Val	Leu	Glu	Lys	
				245						250					255		
	AAT	GTC	CAA	TTA	GAA	GAA	CAG	ATT	TCT	GAC	TTA	CAC	AAG	AGC	CTA	GAA	816
	Asn	Val	Gln	Leu	Glu	Glu	Gln	Ile	Ser	Asp	Leu	His	Lys	Ser	Leu	Glu	
				260					265					270			
30	CAG	AAA	GAA	AGT	AAA	ATC	CAG	CAG	CTA	GCA	GAA	ACT	ATA	AAG	AAA	CTT	864
	Gln	Lys	Glu	Ser	Lys	Ile	Gln	Gln	Leu	Ala	Glu	Thr	Ile	Lys	Lys	Leu	
			275				280						285				
	GAA	AAG	GAG	TTC	AAG	CAG	TTT	GCA	CAG	TTG	TTT	GGC	AAA	AAT	GGA	AGC	912
35	Glu	Lys	Glu	Phe	Lys	Gln	Phe	Ala	Gln	Leu	Phe	Gly	Lys	Asn	Gly	Ser	
		290					295					300					
	TTC	CTC	CCA	AAC	ATC	CAG	GTT	TTT	GCC	AGT	CAC	ATT	GAC	AAG	TCA	GCT	960
	Phe	Leu	Pro	Asn	Ile	Gln	Val	Phe	Ala	Ser	His	Ile	Asp	Lys	Ser	Ala	
		305				310					315					320	
40	TGG	CTA	GAA	GCT	CAA	GTG	CAT	CAA	TTA	TTA	CAA	ATG	GTT	AAC	CAG	CAA	1008
	Trp	Leu	Glu	Ala	Gln	Val	His	Gln	Leu	Leu	Gln	Met	Val	Asn	Gln	Gln	
				325					330						335		
	CAA	AAT	AAA	TTT	GAC	CTG	AGA	CCT	TTG	ATG	GAA	GCA	GTT	GAT	ACA	GTG	1056
	Gln	Asn	Lys	Phe	Asp	Leu	Arg	Pro	Leu	Met	Glu	Ala	Val	Asp	Thr	Val	
				340					345					350			
45	AAA	CAG	AAA	ATT	ACC	CTG	CTA	GAA	AAC	AAT	GAT	CAA	AGA	TTA	GCC	GTT	1104
	Lys	Gln	Lys	Ile	Thr	Leu	Leu	Glu	Asn	Asn	Asp	Gln	Arg	Leu	Ala	Val	
			355					360					365				
	TTA	GAA	GAG	GAA	ACT	AAC	AAA	CAT	GAT	ACC	CAC	ATT	AAT	ATT	CAT	AAA	1152
	Leu	Glu	Glu	Glu	Thr	Asn	Lys	His	Asp	Thr	His	Ile	Asn	Ile	His	Lys	
50		370					375					380					
55																	

5
10
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30
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40
45
50
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GCA CAG CTG AGT AAA AAT GAA GAG CGA TTT AAA CTG CTG GAG GGT ACT 1200
Ala Gln Leu Ser Lys Asn Glu Glu Arg Phe Lys Leu Leu Glu Gly Thr
385 390 395 400

TGC TAT AAT GGA AAG CTC ATT TGG AAG GTG ACA GAT TAC AAG ATG AAG 1248
Cys Tyr Asn Gly Lys Leu Ile Trp Lys Val Thr Asp Tyr Lys Met Lys
405 410 415

AAG AGA GAG GCG GTG GAT GGG CAC ACA GTG TCC ATC TTC AGC CAG TCC 1296
Lys Arg Glu Ala Val Asp Gly His Thr Val Ser Ile Phe Ser Gln Ser
420 425 430

TTC TAC ACC AGC CGC TGT GGC TAC CGG CTC TGT GCT AGA GCA TAC CTG 1344
Phe Tyr Thr Ser Arg Cys Gly Tyr Arg Leu Cys Ala Arg Ala Tyr Leu
435 440 445

AAT GGG GAT GGG TCA GGG AGG GGG TCA CAC CTG TCC CTA TAC TTT GTG 1392
Asn Gly Asp Gly Ser Gly Arg Gly Ser His Leu Ser Leu Tyr Phe Val
450 455 460

GTC ATG CGA GGA GAG TTT GAC TCA CTG TTG CAG TGG CCA TTC AGG CAG 1440
Val Met Arg Gly Glu Phe Asp Ser Leu Leu Gln Trp Pro Phe Arg Gln
465 470 475 480

AGG GTG ACC CTG ATG CTT CTG GAC CAG AGT GGC AAA AAG AAC ATT ATG 1488
Arg Val Thr Leu Met Leu Leu Asp Gln Ser Gly Lys Lys Asn Ile Met
485 490 495

GAG ACC TTC AAA CCT GAC CCC AAT AGC AGC AGC TTT AAA AGA CCT GAT 1536
Glu Thr Phe Lys Pro Asp Pro Asn Ser Ser Ser Phe Lys Arg Pro Asp
500 505 510

GGG GAG ATG AAC ATT GCA TCT GGC TGT CCC CGC TTT GTG GCT CAT TCT 1584
Gly Glu Met Asn Ile Ala Ser Gly Cys Pro Arg Phe Val Ala His Ser
515 520 525

GTT TTG GAG AAT GCC AAG AAC GCC TAC ATT AAA GAT GAC ACT CTG TTC 1632
Val Leu Glu Asn Ala Lys Asn Ala Tyr Ile Lys Asp Asp Thr Leu Phe
530 535 540

TTG AAA GTG GCC GTG GAC TTA ACT GAC CTG GAG GAT CTC 1671
Leu Lys Val Ala Val Asp Leu Thr Asp Leu Glu Asp Leu
545 550 555

SEQ ID NO : 6
LENGTH : 3993
TYPE : nucleic acid
STRANDNESS : double
TOPOLOGY : linear
MOLECULE TYPE : cDNA to mRNA
ORIGINAL SOURCE
ORGANISM : human
IMMEDIATE SOURCE
CLONE : pBShtRAF5
FEATURE
Feature Key : CDS
Location : 55..1725
Method for the determination of feature : P
SEQUENCE DESCRIPTION

GCAGCAGCCG CGCCTGCAGA CCGCCTCGC GGAGCCCGCG CGCCGAGCCC CACA ATG 57
Met
1

GCT TAT TCA GAA GAG CAT AAA GGT ATG CCC TGT GGT TTC ATC CGC CAG 105

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	Ala	Tyr	Ser	Glu	Glu	His	Lys	Gly	Met	Pro	Cys	Gly	Phe	Ile	Arg	Gln	
				5					10					15			
5	AAT	TCC	GGC	AAC	TCC	ATT	TCC	TTG	GAC	TTT	GAG	CCC	AGT	ATA	GAG	TAC	153
	Asn	Ser	Gly	Asn	Ser	Ile	Ser	Leu	Asp	Phe	Glu	Pro	Ser	Ile	Glu	Tyr	
			20					25					30				
	CAG	TTT	GTG	GAG	CGG	TTG	GAA	GAG	CGC	TAC	AAA	TGT	GCC	TTC	TGC	CAC	201
	Gln	Phe	Val	Glu	Arg	Leu	Glu	Glu	Arg	Tyr	Lys	Cys	Ala	Phe	Cys	His	
			35				40					45					
10	TCG	GTG	CTT	CAC	AAC	CCC	CAC	CAG	ACA	GGA	TGT	GGG	CAC	CGC	TTC	TGC	249
	Ser	Val	Leu	His	Asn	Pro	His	Gln	Thr	Gly	Cys	Gly	His	Arg	Phe	Cys	
	50					55					60					65	
	CAG	CAC	TGC	ATC	CTG	TCC	CTG	AGA	GAA	TTA	AAC	ACA	GTG	CCA	ATC	TGC	297
	Gln	His	Cys	Ile	Leu	Ser	Leu	Arg	Glu	Leu	Asn	Thr	Val	Pro	Ile	Cys	
15					70					75					80		
	CCT	GTA	GAT	AAA	GAG	GTC	ATC	AAA	TCT	CAG	GAG	GTT	TTT	AAA	GAC	AAT	345
	Pro	Val	Asp	Lys	Glu	Val	Ile	Lys	Ser	Gln	Glu	Val	Phe	Lys	Asp	Asn	
				85				90						95			
	TGT	TGC	AAA	AGA	GAA	GTC	CTC	AAC	TTA	TAT	GTA	TAT	TGC	AGC	AAT	GCT	393
20	Cys	Cys	Lys	Arg	Glu	Val	Leu	Asn	Leu	Tyr	Val	Tyr	Cys	Ser	Asn	Ala	
			100					105					110				
	CCT	GGA	TGT	AAT	GCC	AAG	GTT	ATT	CTG	GGC	CGG	TAC	CAG	GAT	CAC	CTT	441
	Pro	Gly	Cys	Asn	Ala	Lys	Val	Ile	Leu	Gly	Arg	Tyr	Gln	Asp	His	Leu	
		115					120					125					
25	CAG	CAG	TGC	TTA	TTT	CAA	CCT	GTG	CAG	TGT	TCT	AAT	GAG	AAG	TGC	CGG	489
	Gln	Gln	Cys	Leu	Phe	Gln	Pro	Val	Gln	Cys	Ser	Asn	Glu	Lys	Cys	Arg	
			130			135					140					145	
	GAG	CCA	GTC	CTA	CGG	AAA	GAC	CTG	AAA	GAG	CAT	TTG	AGT	GCA	TCC	TGT	537
	Glu	Pro	Val	Leu	Arg	Lys	Asp	Leu	Lys	Glu	His	Leu	Ser	Ala	Ser	Cys	
				150					155						160		
30	CAG	TTT	CGA	AAG	GAA	AAA	TGC	CTT	TAT	TGC	AAA	AAG	GAT	GTG	GTA	GTC	585
	Gln	Phe	Arg	Lys	Glu	Lys	Cys	Leu	Tyr	Cys	Lys	Lys	Asp	Val	Val	Val	
			165					170					175				
	ATC	AAT	CTA	CAG	AAT	CAT	GAG	GAA	AAC	TTG	TGT	CCT	GAA	TAC	CCA	GTA	633
35	Ile	Asn	Leu	Gln	Asn	His	Glu	Glu	Asn	Leu	Cys	Pro	Glu	Tyr	Pro	Val	
			180					185					190				
	TTT	TGT	CCC	AAC	AAT	TGT	GCG	AAG	ATT	ATT	CTA	AAA	ACT	GAG	GTA	GAT	681
	Phe	Cys	Pro	Asn	Asn	Cys	Ala	Lys	Ile	Ile	Leu	Lys	Thr	Glu	Val	Asp	
			195			200						205					
	GAA	CAC	CTG	GCT	GTA	TGT	CCT	GAA	GCT	GAG	CAA	GAC	TGT	CCT	TTT	AAG	729
40	Glu	His	Leu	Ala	Val	Cys	Pro	Glu	Ala	Glu	Gln	Asp	Cys	Pro	Phe	Lys	
			210			215					220					225	
	CAC	TAT	GGC	TGT	GCT	GTA	ACG	GAT	AAA	CGG	AGG	AAC	CTG	CAG	CAA	CAT	777
	His	Tyr	Gly	Cys	Ala	Val	Thr	Asp	Lys	Arg	Arg	Asn	Leu	Gln	Gln	His	
				230					235						240		
45	GAG	CAT	TCA	GCC	TTA	CGG	GAG	CAC	ATG	CGT	TTG	GTT	TTA	GAA	AAG	AAT	825
	Glu	His	Ser	Ala	Leu	Arg	Glu	His	Met	Arg	Leu	Val	Leu	Glu	Lys	Asn	
				245					250					255			
	GTC	CAA	TTA	GAA	GAA	CAG	ATT	TCT	GAC	TTA	CAC	AAG	AGC	CTA	GAA	CAG	873
	Val	Gln	Leu	Glu	Glu	Gln	Ile	Ser	Asp	Leu	His	Lys	Ser	Leu	Glu	Gln	
50			260				265						270				
55																	

5	AAA GAA AGT AAA ATC CAG CAG CTA GCA GAA ACT ATA AAG AAA CTT GAA Lys Glu Ser Lys Ile Gln Gln Leu Ala Glu Thr Ile Lys Lys Leu Glu 275 280 285	921
10	AAG GAG TTC AAG CAG TTT GCA CAG TTG TTT GGC AAA AAT GGA AGC TTC Lys Glu Phe Lys Gln Phe Ala Gln Leu Phe Gly Lys Asn Gly Ser Phe 290 295 300 305	969
15	CTC CCA AAC ATC CAG GTT TTT GCC AGT CAC ATT GAC AAG TCA GCT TGG Leu Pro Asn Ile Gln Val Phe Ala Ser His Ile Asp Lys Ser Ala Trp 310 315 320	1017
20	CTA GAA GCT CAA GTG CAT CAA TTA TTA CAA ATG GTT AAC CAG CAA CAA Leu Glu Ala Gln Val His Gln Leu Leu Gln Met Val Asn Gln Gln Gln 325 330 335	1065
25	AAT AAA TTT GAC CTG AGA CCT TTG ATG GAA GCA GTT GAT ACA GTG AAA Asn Lys Phe Asp Leu Arg Pro Leu Met Glu Ala Val Asp Thr Val Lys 340 345 350	1113
30	CAG AAA ATT ACC CTG CTA GAA AAC AAT GAT CAA AGA TTA GCC GTT TTA Gln Lys Ile Thr Leu Leu Glu Asn Asn Asp Gln Arg Leu Ala Val Leu 355 360 365	1161
35	GAA GAG GAA ACT AAC AAA CAT GAT ACC CAC ATT AAT ATT CAT AAA GCA Glu Glu Glu Thr Asn Lys His Asp Thr His Ile Asn Ile His Lys Ala 370 375 380 385	1209
40	CAG CTG AGT AAA AAT GAA GAG CGA TTT AAA CTG CTG GAG GGT ACT TGC Gln Leu Ser Lys Asn Glu Glu Arg Phe Lys Leu Leu Glu Gly Thr Cys 390 395 400	1257
45	TAT AAT GGA AAG CTC ATT TGG AAG GTG ACA GAT TAC AAG ATG AAG AAG Tyr Asn Gly Lys Leu Ile Trp Lys Val Thr Asp Tyr Lys Met Lys Lys 405 410 415	1305
50	AGA GAG GCG GTG GAT GGG CAC ACA GTG TOC ATC TTC AGC CAG TCC TTC Arg Glu Ala Val Asp Gly His Thr Val Ser Ile Phe Ser Gln Ser Phe 420 425 430	1353
55	TAC ACC AGC CGC TGT GGC TAC CGG CTC TGT GCT AGA GCA TAC CTG AAT Tyr Thr Ser Arg Cys Gly Tyr Arg Leu Cys Ala Arg Ala Tyr Leu Asn 435 440 445	1401
60	GGG GAT GGG TCA GGG AGG GGG TCA CAC CTG TCC CTA TAC TTT GTG GTC Gly Asp Gly Ser Gly Arg Gly Ser His Leu Ser Leu Tyr Phe Val Val 450 455 460 465	1449
65	ATG CGA GGA GAG TTT GAC TCA CTG TTG CAG TGG CCA TTC AGG CAG AGG Met Arg Gly Glu Phe Asp Ser Leu Leu Gln Trp Pro Phe Arg Gln Arg 470 475 480	1497
70	GTG ACC CTG ATG CTT CTG GAC CAG AGT GGC AAA AAG AAC ATT ATG GAG Val Thr Leu Met Leu Leu Asp Gln Ser Gly Lys Lys Asn Ile Met Glu 485 490 495	1545
75	ACC TTC AAA CCT GAC CCC AAT AGC AGC AGC TTT AAA AGA CCT GAT GGG Thr Phe Lys Pro Asp Pro Asn Ser Ser Ser Phe Lys Arg Pro Asp Gly 500 505 510	1593
80	GAG ATG AAC ATT GCA TCT GGC TGT CCC CGC TTT GTG GCT CAT TCT GTT Glu Met Asn Ile Ala Ser Gly Cys Pro Arg Phe Val Ala His Ser Val 515 520 525	1641
85	TTG GAG AAT GCC AAG AAC GCC TAC ATT AAA GAT GAC ACT CTG TTC TTG Leu Glu Asn Ala Lys Asn Ala Tyr Ile Lys Asp Asp Thr Leu Phe Leu 530 535 540 545	1689

	AAA GTG GCC GTG GAC TTA ACT GAC CTG GAG GAT CTC TAGTCACTGT	1735
	Lys Val Ala Val Asp Leu Thr Asp Leu Glu Asp Leu	
	550 555	
5	TATGGGGTGA TAAGAGGACT TCTTGGGGCC AGAACTGTGG AGGAGAGCAC ATTTGATTAT	1795
	CATATTGACC TGGATTTAGA CTCAAAGCAC ATTTGTATTT GCCTTTTTC TTAACGTTTG	1855
	AAGTCAGTTT AAAACTTCTG AAGTGCTGTC TTTTACATT TTA CTCTGTC CCAGTTTGAA	1915
10	ACTTAAACT CTTAGAATAT TCTCTTATTA TTTATATTTT TATATTTCTT GAAAGATGGT	1975
	AAGTTTCTTG AAGTTTTTGG GGC GTTCTC TTTTACTGGT GCTTAGCGCA GTGTCTCGGG	2035
	CACTCTAAAT ATTGAGTGT ATGGAGGACA CAGAGGTAGC AGAATCCAG TTGAAAATGT	2095
15	TTTGATATTT TATTGTTTGG CCTATTGATT CTAGACCTGG CCTTAAGTCT GCAAAAGCCA	2155
	TCTTTATAAG GTAGGCTGTT CCAGTTAAGA AGTGGGTGAT GTAGTTACAA AGATAATATG	2215
	CTCAGTTTGG ACCTTTTTTT CAGTTAAATG CTAAATATAT GAAAATTACT ATACCTCTAA	2275
	GTATTTTCAT GAAATTCACC AGCAGTTTGC AAGCACAGTT TTGCAAGGCT GCATAAGAAC	2335
20	TGGTGAATGG GGTAAAGCATT TTCATTCTTC CTGCTGAAGT AAAGCAGAAA GTACTGCATA	2395
	GTATATGAGA TATAGCCAGC TAGCTAAAGT TCAGATTTTG TTAGGTTCAA CCCTATGAAA	2455
	AAACTATTT TCATAGGTCA AAAATGGTAA AAAATTAGCA GTTTCATAAG ATTCAACCAA	2515
25	ATAAATATAT ATATACACAC ACACATACAT ATACACCTAT ATATGTGTGT ATACAAACAG	2575
	TTCGAATGTA TTTTGGTGAC AGTAATAAAT CAATGTGAGG ATGGATAGAA TTTAGTATAT	2635
	GATAGAGAAA ATGTCATAAA TGGATAAAAG GAATTTACAA CTGAGGAGA AAACCTTTAC	2695
	AATTTCTAT GGGGTGCAGA AGTACTCTCA GCGAAAAC TG GCTAAAA CAGTATCTAC	2755
30	TATTCTCTGA TAACTTTTTT TTTGAGACAG AGTTTCATTG TCACCCAGGC TGGAGTACAG	2815
	TGGCATGATC TCAGCTCACT GCAAACCTG CCTCCCGAAT TCAAGTGATT CTCCTGCCTC	2875
	AGCCTCCTGA GTAGCTGGGA TTACAGGCGC CCGTCACCAC ACCCAGGTAA TTTTGTATT	2935
35	TTTAGTAGAG ACGGAGTTTT GCCATGTTGG CCAAGCTGAT CTCAAACCTC TGACCTCAAG	2995
	TGATCTGOC GCCTCGGCCT CCCAAAGTGC TGAGATTACA GGCATGACCC ACCGCGTCAA	3055
	GCCTCTGACA ACTATTGAAT TTGTAAGCTG CTATGCAAAT GGGCATTAT ATAACTTGT	3115
	GATGTTTCTT GTCAGAATTC TGAGTACTCT GTGAAGAACA GAAATGATCA TATTCTTATG	3175
40	CATCTATCTG TATGGGCTG AAGGTGTATA TACAACTGA GATGAGTCCT TATGACTCTT	3235
	GATAAGCCTG AGTTTAACAA CAACAAAAAT GCCAAGTTGT CCTGAGCCCT TCTGCGTTGT	3295
	TATGCCACTT CCCTACTGCT CATATGCACG CTGGCTCCCC TGGGCACGCA AGGATGAGTA	3355
45	TGGGOCATGG GCCCCTGTAG AGCTGCTTAC CTGGTGATGA CCATGCACCT TACAATTTCT	3415
	GAACAGTTAA CCCTATAGAA GCATGCTTTA TATGAGTGT TCTGGGAAG AGGAACCTTC	3475
	TTAATCTCTT CTGTGGGATT TTCAAAATGC TAAAGACTCA CACTGCAGCA ATCATCCCAG	3535
50	ATGATTAAAT TCAAAGAAAT AGGTTCAAA CAGGAATATA CTGAAGAACT AGAGTGTAC	3595
55		

TGCTGGTGAA CTGTGGCAG GTTGCTCAAC ACATCACCTC GGACAAATTC AGGAAGCATT 3655
TCTTTAGCCC ACAAGTCCAG ACCCAGGTGC TCTGTATGTT TGTTTTTAAT ATTCATCATA 3715
5 TCCAAGTTCA CTCTGTCTTC CTGAGCAGTG GAAGATCATA TTGCTGTAAC TTCTTTTAAG 3775
TAGTTGATGT GGAAAACATT TTAAAGTGAA TTTGTCAAAA TGCTGGTTTT GTGTTTTATC 3835
CAACTTTTGT GCATATATAT AAAGTATGTC ATGGCATGGT TTGCTTAGGA GTTCAGAGTT 3895
10 CCTTCATCAT CGAAATAGTG ATTAAGTGAT CCCAGAACAA GGAATACTAG AGTAAAAAGC 3955
ACCTCTTTTT CAGAAAAAAA AAAAAAAAAA AAAAAAAA 3993

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SEQUENCE LISTING

5 (1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: MOCHIDA PHARMACEUTICAL CO., LTD
 (B) STREET: 7, Yotsuya 1-chome, Shinjuku-ku
 (C) CITY: Tokyo
 (E) COUNTRY: Japan
 (F) POSTAL CODE (ZIP): 160

(ii) TITLE OF INVENTION: NOVEL SIGNAL TRANSDUCER

(iii) NUMBER OF SEQUENCES: 12

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
 (B) COMPUTER: IBM PC compatible
 (C) OPERATING SYSTEM: PC-DOS/MS-DOS
 (D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(v) CURRENT APPLICATION DATA:

APPLICATION NUMBER: EP 97915700.5

25 (2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 558 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Met Ala His Ser Glu Glu Gln Ala Ala Val Pro Cys Ala Phe Ile Arg
 1 5 10 15
 Gln Asn Ser Gly Asn Ser Ile Ser Leu Asp Phe Glu Pro Asp Thr Glu
 20 25 30
 Tyr Gln Phe Val Glu Gln Leu Glu Glu Arg Tyr Lys Cys Ala Phe Cys
 35 40 45
 His Ser Val Leu His Asn Pro His Gln Thr Gly Cys Gly His Arg Phe
 50 55 60
 Cys Gln Gln Cys Ile Arg Ser Leu Arg Glu Leu Asn Ser Val Pro Ile
 65 70 75 80
 Cys Pro Val Asp Lys Glu Val Ile Lys Pro Gln Glu Val Phe Lys Asp
 85 90 95

Asn Cys Cys Lys Arg Glu Val Leu Asn Leu His Val Tyr Cys Lys Asn
 100 105 110
 5 Ala Pro Gly Cys Asn Ala Arg Ile Ile Leu Gly Arg Phe Gln Asp His
 115 120 125
 Leu Gln His Cys Ser Phe Gln Ala Val Pro Cys Pro Asn Glu Ser Cys
 130 135 140
 10 Arg Glu Ala Met Leu Arg Lys Asp Val Lys Glu His Leu Ser Ala Tyr
 145 150 155 160
 Cys Arg Phe Arg Glu Glu Lys Cys Leu Tyr Cys Lys Arg Asp Ile Val
 165 170 175
 15 Val Thr Asn Leu Gln Asp His Glu Glu Asn Ser Cys Pro Ala Tyr Pro
 180 185 190
 Val Ser Cys Pro Asn Arg Cys Val Gln Thr Ile Pro Arg Ala Arg Val
 195 200 205
 20 Asn Glu His Leu Thr Val Cys Pro Glu Ala Glu Gln Asp Cys Pro Phe
 210 215 220
 25 Lys His Tyr Gly Cys Thr Val Lys Gly Lys Arg Gly Asn Leu Leu Glu
 225 230 235 240
 His Glu Arg Ala Ala Leu Gln Asp His Met Leu Leu Val Leu Glu Lys
 245 250 255
 30 Asn Tyr Gln Leu Glu Gln Arg Ile Ser Asp Leu Tyr Gln Ser Leu Glu
 260 265 270
 Gln Lys Glu Ser Lys Ile Gln Gln Leu Ala Glu Thr Val Lys Lys Phe
 275 280 285
 35 Glu Lys Glu Leu Lys Gln Phe Thr Gln Met Phe Gly Arg Asn Gly Thr
 290 295 300
 Phe Leu Ser Asn Val Gln Ala Leu Thr Ser His Thr Asp Lys Ser Ala
 305 310 315 320
 Trp Leu Glu Ala Gln Val Arg Gln Leu Leu Gln Ile Val Asn Gln Gln
 325 330 335
 40 Pro Ser Arg Leu Asp Leu Arg Ser Leu Val Asp Ala Val Asp Ser Val
 340 345 350
 Lys Gln Arg Ile Thr Gln Leu Glu Ala Ser Asp Gln Arg Leu Val Leu
 355 360 365
 50 Leu Glu Gly Glu Thr Ser Lys His Asp Ala His Ile Asn Ile His Lys
 370 375 380
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Ala Gln Leu Asn Lys Asn Glu Glu Arg Phe Lys Gln Leu Glu Gly Ala
 385 390 395 400

5 Cys Tyr Ser Gly Lys Leu Ile Trp Lys Val Thr Asp Tyr Arg Val Lys
 405 410 415

Lys Arg Glu Ala Val Glu Gly His Thr Val Ser Val Phe Ser Gln Pro
 420 425 430

10 Phe Tyr Thr Ser Arg Cys Gly Tyr Arg Leu Cys Ala Arg Ala Tyr Leu
 435 440 445

Asn Gly Asp Gly Ser Gly Lys Gly Thr His Leu Ser Leu Tyr Phe Val
 450 455 460

15 Val Met Arg Gly Glu Phe Asp Ser Leu Leu Gln Trp Pro Phe Arg Gln
 465 470 475 480

Arg Val Thr Leu Met Leu Leu Asp Gln Ser Gly Lys Lys Asn His Ile
 485 490 495

20 Val Glu Thr Phe Lys Ala Asp Pro Asn Ser Ser Ser Phe Lys Arg Pro
 500 505 510

25 Asp Gly Glu Met Asn Ile Ala Ser Gly Cys Pro Arg Phe Val Ser His
 515 520 525

Ser Thr Leu Glu Asn Ser Lys Asn Thr Tyr Ile Lys Asp Asp Thr Leu
 530 535 540

30 Phe Leu Lys Val Ala Val Asp Leu Thr Asp Leu Glu Asp Leu
 545 550 555

(2) INFORMATION FOR SEQ ID NO: 2:

35 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1674 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

40 (ii) MOLECULE TYPE: cDNA to mRNA

(ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 1..1674

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

50 ATG GCT CAT TCG GAG GAG CAA GCG GCT GTC CCC TGC GCC TTC ATC CGC 48
 Met Ala His Ser Glu Glu Gln Ala Ala Val Pro Cys Ala Phe Ile Arg
 1 5 10 15

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EP 0 915 155 A1

	CAG AAC TCT GGC AAC TCA ATT TCC TTG GAC TTT GAG CCC GAC ACC GAG	96
	Gln Asn Ser Gly Asn Ser Ile Ser Leu Asp Phe Glu Pro Asp Thr Glu	
	20 25 30	
5	TAC CAG TTT GTG GAG CAG CTG GAA GAA CGC TAC AAA TGT GCC TTC TGC	144
	Tyr Gln Phe Val Glu Gln Leu Glu Glu Arg Tyr Lys Cys Ala Phe Cys	
	35 40 45	
10	CAC TCC GTG CTT CAC AAC CCC CAC CAG ACC GGC TGC GGG CAC CGC TTC	192
	His Ser Val Leu His Asn Pro His Gln Thr Gly Cys Gly His Arg Phe	
	50 55 60	
	TGC CAG CAG TGC ATC CGG TCT CTG AGA GAA TTG AAC TCG GTG CCG ATC	240
15	Cys Gln Gln Cys Ile Arg Ser Leu Arg Glu Leu Asn Ser Val Pro Ile	
	65 70 75 80	
	TGC CCG GTA GAC AAG GAG GTC ATC AAG CCT CAG GAG GTG TTC AAA GAC	288
	Cys Pro Val Asp Lys Glu Val Ile Lys Pro Gln Glu Val Phe Lys Asp	
	85 90 95	
20	AAC TGC TGC AAA AGA GAA GTT CTC AAT TTA CAC GTC TAC TGC AAA AAC	336
	Asn Cys Cys Lys Arg Glu Val Leu Asn Leu His Val Tyr Cys Lys Asn	
	100 105 110	
25	GCC CCC GGG TGC AAT GCC AGG ATT ATT CTG GGA CGA TTC CAG GAC CAC	384
	Ala Pro Gly Cys Asn Ala Arg Ile Ile Leu Gly Arg Phe Gln Asp His	
	115 120 125	
	CTT CAG CAC TGT TCC TTC CAA GCC GTG CCC TGC CCT AAC GAG AGC TGC	432
30	Leu Gln His Cys Ser Phe Gln Ala Val Pro Cys Pro Asn Glu Ser Cys	
	130 135 140	
	CGG GAA GCC ATG CTC CGG AAA GAC GTG AAA GAG CAC CTG AGC GCA TAC	480
	Arg Glu Ala Met Leu Arg Lys Asp Val Lys Glu His Leu Ser Ala Tyr	
	145 150 155 160	
35	TGC CGG TTC CGA GAG GAG AAG TGC CTT TAC TGC AAA AGG GAC ATA GTG	528
	Cys Arg Phe Arg Glu Glu Lys Cys Leu Tyr Cys Lys Arg Asp Ile Val	
	165 170 175	
40	GTG ACC AAC CTG CAG GAT CAT GAG GAA AAC TCG TGT CCT GCG TAC CCA	576
	Val Thr Asn Leu Gln Asp His Glu Glu Asn Ser Cys Pro Ala Tyr Pro	
	180 185 190	
	GTG TCT TGT CCC AAC AGG TGT GTG CAG ACT ATT CCA AGA GCT AGG GTG	624
45	Val Ser Cys Pro Asn Arg Cys Val Gln Thr Ile Pro Arg Ala Arg Val	
	195 200 205	
	AAT GAA CAC CTT ACT GTA TGT CCT GAG GCT GAG CAA GAC TGT CCC TTT	672
	Asn Glu His Leu Thr Val Cys Pro Glu Ala Glu Gln Asp Cys Pro Phe	
	210 215 220	
50	AAG CAC TAT GGC TGC ACT GTC AAG GGT AAG CGG GGG AAC TTG CTG GAG	720
	Lys His Tyr Gly Cys Thr Val Lys Gly Lys Arg Gly Asn Leu Leu Glu	
	225 230 235 240	
55		

	CAT GAG CGG GCA GCC CTG CAG GAC CAC ATG CTT CTG GTT TTA GAG AAG	768
	His Glu Arg Ala Ala Leu Gln Asp His Met Leu Leu Val Leu Glu Lys	
	245 250 255	
5	AAC TAC CAA CTA GAA CAG CGG ATC TCT GAT TTA TAT CAG AGT CTC GAA	816
	Asn Tyr Gln Leu Glu Gln Arg Ile Ser Asp Leu Tyr Gln Ser Leu Glu	
	260 265 270	
10	CAG AAG GAA AGC AAG ATC CAG CAG CTG GCA GAA ACC GTG AAG AAG TTC	864
	Gln Lys Glu Ser Lys Ile Gln Gln Leu Ala Glu Thr Val Lys Lys Phe	
	275 280 285	
15	GAA AAG GAG CTT AAG CAG TTC ACA CAG ATG TTT GGC AGA AAT GGA ACT	912
	Glu Lys Glu Leu Lys Gln Phe Thr Gln Met Phe Gly Arg Asn Gly Thr	
	290 295 300	
	TTC CTC TCA AAT GTC CAG GCT CTC ACC AGT CAC ACG GAC AAG TCA GCT	960
	Phe Leu Ser Asn Val Gln Ala Leu Thr Ser His Thr Asp Lys Ser Ala	
	305 310 315 320	
20	TGG CTG GAA GCG CAG GTG CGG CAG CTG CTA CAA ATA GTT AAC CAG CAG	1008
	Trp Leu Glu Ala Gln Val Arg Gln Leu Leu Gln Ile Val Asn Gln Gln	
	325 330 335	
25	CCA AGT CGA CTT GAT CTG AGG TCT TTG GTG GAT GCG GTT GAC AGC GTG	1056
	Pro Ser Arg Leu Asp Leu Arg Ser Leu Val Asp Ala Val Asp Ser Val	
	340 345 350	
30	AAA CAG AGG ATC ACC CAG CTG GAA GCC AGT GAC CAG AGA TTA GTT CTT	1104
	Lys Gln Arg Ile Thr Gln Leu Glu Ala Ser Asp Gln Arg Leu Val Leu	
	355 360 365	
	TTA GAG GGG GAG ACC AGC AAG CAC GAC GCA CAC ATT AAT ATC CAC AAA	1152
	Leu Glu Gly Glu Thr Ser Lys His Asp Ala His Ile Asn Ile His Lys	
	370 375 380	
35	GCA CAG CTG AAT AAG AAC GAA GAG CGG TTT AAG CAG CTG GAG GGC GCC	1200
	Ala Gln Leu Asn Lys Asn Glu Glu Arg Phe Lys Gln Leu Glu Gly Ala	
	385 390 395 400	
40	TGC TAC AGT GGC AAG CTC ATC TGG AAG GTG ACA GAT TAC AGG GTG AAG	1248
	Cys Tyr Ser Gly Lys Leu Ile Trp Lys Val Thr Asp Tyr Arg Val Lys	
	405 410 415	
45	AAG AGG GAG GCC GTG GAG GGG CAC ACA GTG TCC GTC TTC AGC CAG CCT	1296
	Lys Arg Glu Ala Val Glu Gly His Thr Val Ser Val Phe Ser Gln Pro	
	420 425 430	
	TTC TAC ACC AGC CGC TGC GGC TAC CGG CTC TGT GCC AGG GCG TAC CTG	1344
	Phe Tyr Thr Ser Arg Cys Gly Tyr Arg Leu Cys Ala Arg Ala Tyr Leu	
	435 440 445	
50	AAC GGG GAC GGG TCG GGG AAG GGA ACG CAC CTG TCC CTG TAC TTT GTG	1392
	Asn Gly Asp Gly Ser Gly Lys Gly Thr His Leu Ser Leu Tyr Phe Val	
	450 455 460	

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GTG ATG CGC GGT GAG TTT GAC TCG CTG CTG CAG TGG CCG TTC AGG CAG 1440
 Val Met Arg Gly Glu Phe Asp Ser Leu Leu Gln Trp Pro Phe Arg Gln
 465 470 475 480

AGG GTG ACC CTG ATG CTT TTG GAC CAG AGC GGC AAG AAG AAC CAT ATT 1488
 Arg Val Thr Leu Met Leu Leu Asp Gln Ser Gly Lys Lys Asn His Ile
 485 490 495

GTG GAG ACC TTC AAA GCT GAC CCC AAC AGC AGC AGC TTC AAA AGG CCA 1536
 Val Glu Thr Phe Lys Ala Asp Pro Asn Ser Ser Ser Phe Lys Arg Pro
 500 505 510

GAT GGC GAG ATG AAC ATT GCC TCT GGC TGT CCC CGC TTT GTG TCG CAC 1584
 Asp Gly Glu Met Asn Ile Ala Ser Gly Cys Pro Arg Phe Val Ser His
 515 520 525

TCT ACT CTG GAG AAC TCC AAG AAC ACC TAC ATT AAA GAC GAC ACA CTG 1632
 Ser Thr Leu Glu Asn Ser Lys Asn Thr Tyr Ile Lys Asp Asp Thr Leu
 530 535 540

TTC TTG AAA GTG GCC GTG GAT TTA ACT GAC TTG GAG GAT CTG 1674
 Phe Leu Lys Val Ala Val Asp Leu Thr Asp Leu Glu Asp Leu
 545 550 555

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2105 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 188..1861

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

TGTGAGCCGG AGGCGTGTGT GGTAGCGGGC GAACTGAGGC GACGCGGGAC ACCCGCGCCC 60

GGCCGAGGGC ACTTTTGCAA GACTTGTGAG CACAGCCCGT TAACGTGAGC TTAATGCCAG 120

GGTCTCGAGC CTGCGCCGGT GCTATAGCGC GTGCTCGATT GGAAACAGAA CCCGACTCTG 180

CAGAAGA ATG GCT CAT TCG GAG GAG CAA GCG GCT GTC CCC TGC GCC TTC 229

Met Ala His Ser Glu Glu Gln Ala Ala Val Pro Cys Ala Phe
 1 5 10

EP 0 915 155 A1

	ATC CGC CAG AAC TCT GGC AAC TCA ATT TCC TTG GAC TTT GAG CCC GAC	277
	Ile Arg Gln Asn Ser Gly Asn Ser Ile Ser Leu Asp Phe Glu Pro Asp	
	15 20 25 30	
5	ACC GAG TAC CAG TTT GTG GAG CAG CTG GAA GAA CGC TAC AAA TGT GCC	325
	Thr Glu Tyr Gln Phe Val Glu Gln Leu Glu Glu Arg Tyr Lys Cys Ala	
	35 40 45	
10	TTC TGC CAC TCC GTG CTT CAC AAC CCC CAC CAG ACC GGC TGC GGG CAC	373
	Phe Cys His Ser Val Leu His Asn Pro His Gln Thr Gly Cys Gly His	
	50 55 60	
	CGC TTC TGC CAG CAG TGC ATC CGG TCT CTG AGA GAA TTG AAC TCG GTG	421
15	Arg Phe Cys Gln Gln Cys Ile Arg Ser Leu Arg Glu Leu Asn Ser Val	
	65 70 75	
	CCG ATC TGC CCG GTA GAC AAG GAG GTC ATC AAG CCT CAG GAG GTG TTC	469
	Pro Ile Cys Pro Val Asp Lys Glu Val Ile Lys Pro Gln Glu Val Phe	
	80 85 90	
20	AAA GAC AAC TGC TGC AAA AGA GAA GTT CTC AAT TTA CAC GTC TAC TGC	517
	Lys Asp Asn Cys Cys Lys Arg Glu Val Leu Asn Leu His Val Tyr Cys	
	95 100 105 110	
25	AAA AAC GCC CCC GGG TGC AAT GCC AGG ATT ATT CTG GGA CGA TTC CAG	565
	Lys Asn Ala Pro Gly Cys Asn Ala Arg Ile Ile Leu Gly Arg Phe Gln	
	115 120 125	
	GAC CAC CTT CAG CAC TGT TCC TTC CAA GCC GTG CCC TGC CCT AAC GAG	613
30	Asp His Leu Gln His Cys Ser Phe Gln Ala Val Pro Cys Pro Asn Glu	
	130 135 140	
	AGC TGC CGG GAA GCC ATG CTC CGG AAA GAC GTG AAA GAG CAC CTG AGC	661
	Ser Cys Arg Glu Ala Met Leu Arg Lys Asp Val Lys Glu His Leu Ser	
	145 150 155	
35	GCA TAC TGC CGG TTC CGA GAG GAG AAG TGC CTT TAC TGC AAA AGG GAC	709
	Ala Tyr Cys Arg Phe Arg Glu Glu Lys Cys Leu Tyr Cys Lys Arg Asp	
	160 165 170	
40	ATA GTG GTG ACC AAC CTG CAG GAT CAT GAG GAA AAC TCG TGT CCT GCG	757
	Ile Val Val Thr Asn Leu Gln Asp His Glu Glu Asn Ser Cys Pro Ala	
	175 180 185 190	
	TAC CCA GTG TCT TGT CCC AAC AGG TGT GTG CAG ACT ATT CCA AGA GCT	805
45	Tyr Pro Val Ser Cys Pro Asn Arg Cys Val Gln Thr Ile Pro Arg Ala	
	195 200 205	
	AGG GTG AAT GAA CAC CTT ACT GTA TGT CCT GAG GCT GAG CAA GAC TGT	853
	Arg Val Asn Glu His Leu Thr Val Cys Pro Glu Ala Glu Gln Asp Cys	
	210 215 220	
50	CCC TTT AAG CAC TAT GGC TGC ACT GTC AAG GGT AAG CGG GGG AAC TTG	901
	Pro Phe Lys His Tyr Gly Cys Thr Val Lys Gly Lys Arg Gly Asn Leu	
	225 230 235	
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	CTG GAG CAT GAG CGG GCA GCC CTG CAG GAC CAC ATG CTT CTG GTT TTA	949
	Leu Glu His Glu Arg Ala Ala Leu Gln Asp His Met Leu Leu Val Leu	
	240 245 250	
5	GAG AAG AAC TAC CAA CTA GAA CAG CGG ATC TCT GAT TTA TAT CAG AGT	997
	Glu Lys Asn Tyr Gln Leu Glu Gln Arg Ile Ser Asp Leu Tyr Gln Ser	
	255 260 265 270	
10	CTC GAA CAG AAG GAA AGC AAG ATC CAG CAG CTG GCA GAA ACC GTG AAG	1045
	Leu Glu Gln Lys Glu Ser Lys Ile Gln Gln Leu Ala Glu Thr Val Lys	
	275 280 285	
15	AAG TTC GAA AAG GAG CTT AAG CAG TTC ACA CAG ATG TTT GGC AGA AAT	1093
	Lys Phe Glu Lys Glu Leu Lys Gln Phe Thr Gln Met Phe Gly Arg Asn	
	290 295 300	
	GGA ACT TTC CTC TCA AAT GTC CAG GCT CTC ACC AGT CAC ACG GAC AAG	1141
	Gly Thr Phe Leu Ser Asn Val Gln Ala Leu Thr Ser His Thr Asp Lys	
	305 310 315	
20	TCA GCT TGG CTG GAA GCG CAG GTG CGG CAG CTG CTA CAA ATA GTT AAC	1189
	Ser Ala Trp Leu Glu Ala Gln Val Arg Gln Leu Leu Gln Ile Val Asn	
	320 325 330	
25	CAG CAG CCA AGT CGA CTT GAT CTG AGG TCT TTG GTG GAT GCG GTT GAC	1237
	Gln Gln Pro Ser Arg Leu Asp Leu Arg Ser Leu Val Asp Ala Val Asp	
	335 340 345 350	
30	AGC GTG AAA CAG AGG ATC ACC CAG CTG GAA GCC AGT GAC CAG AGA TTA	1285
	Ser Val Lys Gln Arg Ile Thr Gln Leu Glu Ala Ser Asp Gln Arg Leu	
	355 360 365	
	GTT CTT TTA GAG GGG GAG ACC AGC AAG CAC GAC GCA CAC ATT AAT ATC	1333
	Val Leu Leu Glu Gly Glu Thr Ser Lys His Asp Ala His Ile Asn Ile	
	370 375 380	
35	CAC AAA GCA CAG CTG AAT AAG AAC GAA GAG CGG TTT AAG CAG CTG GAG	1381
	His Lys Ala Gln Leu Asn Lys Asn Glu Glu Arg Phe Lys Gln Leu Glu	
	385 390 395	
40	GGC GCC TGC TAC AGT GGC AAG CTC ATC TGG AAG GTG ACA GAT TAC AGG	1429
	Gly Ala Cys Tyr Ser Gly Lys Leu Ile Trp Lys Val Thr Asp Tyr Arg	
	400 405 410	
45	GTG AAG AAG AGG GAG GCC GTG GAG GGG CAC ACA GTG TCC GTC TTC AGC	1477
	Val Lys Lys Arg Glu Ala Val Glu Gly His Thr Val Ser Val Phe Ser	
	415 420 425 430	
	CAG CCT TTC TAC ACC AGC CGC TGC GGC TAC CGG CTC TGT GCC AGG GCG	1525
	Gln Pro Phe Tyr Thr Ser Arg Cys Gly Tyr Arg Leu Cys Ala Arg Ala	
	435 440 445	
50	TAC CTG AAC GGG GAC GGG TCG GGG AAG GGA ACG CAC CTG TCC CTG TAC	1573
	Tyr Leu Asn Gly Asp Gly Ser Gly Lys Gly Thr His Leu Ser Leu Tyr	
	450 455 460	

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5 TTT GTG GTG ATG CGC GGT GAG TTT GAC TCG CTG CTG CAG TGG CCG TTC 1621
 Phe Val Val Met Arg Gly Glu Phe Asp Ser Leu Leu Gln Trp Pro Phe
 465 470 475
 10 AGG CAG AGG GTG ACC CTG ATG CTT TTG GAC CAG AGC GGC AAG AAG AAC 1669
 Arg Gln Arg Val Thr Leu Met Leu Leu Asp Gln Ser Gly Lys Lys Asn
 480 485 490
 15 CAT ATT GTG GAG ACC TTC AAA GCT GAC CCC AAC AGC AGC AGC TTC AAA 1717
 His Ile Val Glu Thr Phe Lys Ala Asp Pro Asn Ser Ser Ser Phe Lys
 495 500 505 510
 20 AGG CCA GAT GGC GAG ATG AAC ATT GCC TCT GGC TGT CCC CGC TTT GTG 1765
 Arg Pro Asp Gly Glu Met Asn Ile Ala Ser Gly Cys Pro Arg Phe Val
 515 520 525
 25 TCG CAC TCT ACT CTG GAG AAC TCC AAG AAC ACC TAC ATT AAA GAC GAC 1813
 Ser His Ser Thr Leu Glu Asn Ser Lys Asn Thr Tyr Ile Lys Asp Asp
 530 535 540
 30 ACA CTG TTC TTG AAA GTG GCC GTG GAT TTA ACT GAC TTG GAG GAT CTG 1861
 Thr Leu Phe Leu Lys Val Ala Val Asp Leu Thr Asp Leu Glu Asp Leu
 545 550 555
 TAGTGTACC TGATAAGGAA ACTTCTCAGC ACAGGAAAAG GTGTGGCTGT CCCTTGGGCG 1921
 CAGCCCTCTG GACTGAGCAG GCTCTGTTC TTGTCTTCCT GCCTCCGATG TCTGATGTGT 1981
 CATCTTTTTA TCTTGGATCC TTCCCTGGTT TGAAACTTTA AACTCTTGAA ATATTGCTGT 2041
 TATTTATATT TTTGTATCTT CCAAAAAATT ATAATAATT GACAACAAAA AAAAAAAAAA 2101
 AAAA 2105

35 (2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 557 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

45 (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

50 Met Ala Tyr Ser Glu Glu His Lys Gly Met Pro Cys Gly Phe Ile Arg
 1 5 10 15
 Gln Asn Ser Gly Asn Ser Ile Ser Leu Asp Phe Glu Pro Ser Ile Glu
 20 25 30

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Tyr Gln Phe Val Glu Arg Leu Glu Glu Arg Tyr Lys Cys Ala Phe Cys
 35 40 45
 5 His Ser Val Leu His Asn Pro His Gln Thr Gly Cys Gly His Arg Phe
 50 55 60
 Cys Gln His Cys Ile Leu Ser Leu Arg Glu Leu Asn Thr Val Pro Ile
 65 70 75 80
 10 Cys Pro Val Asp Lys Glu Val Ile Lys Ser Gln Glu Val Phe Lys Asp
 85 90 95
 Asn Cys Cys Lys Arg Glu Val Leu Asn Leu Tyr Val Tyr Cys Ser Asn
 100 105 110
 15 Ala Pro Gly Cys Asn Ala Lys Val Ile Leu Gly Arg Tyr Gln Asp His
 115 120 125
 Leu Gln Gln Cys Leu Phe Gln Pro Val Gln Cys Ser Asn Glu Lys Cys
 130 135 140
 20 Arg Glu Pro Val Leu Arg Lys Asp Leu Lys Glu His Leu Ser Ala Ser
 145 150 155 160
 25 Cys Gln Phe Arg Lys Glu Lys Cys Leu Tyr Cys Lys Lys Asp Val Val
 165 170 175
 Val Ile Asn Leu Gln Asn His Glu Glu Asn Leu Cys Pro Glu Tyr Pro
 180 185 190
 30 Val Phe Cys Pro Asn Asn Cys Ala Lys Ile Ile Leu Lys Thr Glu Val
 195 200 205
 Asp Glu His Leu Ala Val Cys Pro Glu Ala Glu Gln Asp Cys Pro Phe
 210 215 220
 35 Lys His Tyr Gly Cys Ala Val Thr Asp Lys Arg Arg Asn Leu Gln Gln
 225 230 235 240
 His Glu His Ser Ala Leu Arg Glu His Met Arg Leu Val Leu Glu Lys
 245 250 255
 Asn Val Gln Leu Glu Glu Gln Ile Ser Asp Leu His Lys Ser Leu Glu
 260 265 270
 45 Gln Lys Glu Ser Lys Ile Gln Gln Leu Ala Glu Thr Ile Lys Lys Leu
 275 280 285
 Glu Lys Glu Phe Lys Gln Phe Ala Gln Leu Phe Gly Lys Asn Gly Ser
 290 295 300
 50 Phe Leu Pro Asn Ile Gln Val Phe Ala Ser His Ile Asp Lys Ser Ala
 305 310 315 320
 55

Trp Leu Glu Ala Gln Val His Gln Leu Leu Gln Met Val Asn Gln Gln
 325 330 335
 5 Gln Asn Lys Phe Asp Leu Arg Pro Leu Met Glu Ala Val Asp Thr Val
 340 345 350
 Lys Gln Lys Ile Thr Leu Leu Glu Asn Asn Asp Gln Arg Leu Ala Val
 355 360 365
 10 Leu Glu Glu Glu Thr Asn Lys His Asp Thr His Ile Asn Ile His Lys
 370 375 380
 Ala Gln Leu Ser Lys Asn Glu Glu Arg Phe Lys Leu Leu Glu Gly Thr
 385 390 395 400
 15 Cys Tyr Asn Gly Lys Leu Ile Trp Lys Val Thr Asp Tyr Lys Met Lys
 405 410 415
 Lys Arg Glu Ala Val Asp Gly His Thr Val Ser Ile Phe Ser Gln Ser
 420 425 430
 20 Phe Tyr Thr Ser Arg Cys Gly Tyr Arg Leu Cys Ala Arg Ala Tyr Leu
 435 440 445
 Asn Gly Asp Gly Ser Gly Arg Gly Ser His Leu Ser Leu Tyr Phe Val
 450 455 460
 Val Met Arg Gly Glu Phe Asp Ser Leu Leu Gln Trp Pro Phe Arg Gln
 465 470 475 480
 30 Arg Val Thr Leu Met Leu Leu Asp Gln Ser Gly Lys Lys Asn Ile Met
 485 490 495
 Glu Thr Phe Lys Pro Asp Pro Asn Ser Ser Ser Phe Lys Arg Pro Asp
 500 505 510
 35 Gly Glu Met Asn Ile Ala Ser Gly Cys Pro Arg Phe Val Ala His Ser
 515 520 525
 Val Leu Glu Asn Ala Lys Asn Ala Tyr Ile Lys Asp Asp Thr Leu Phe
 530 535 540
 40 Leu Lys Val Ala Val Asp Leu Thr Asp Leu Glu Asp Leu
 545 550 555

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1671 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION:1..1671

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

10 ATG GCT TAT TCA GAA GAG CAT AAA GGT ATG CCC TGT GGT TTC ATC CGC 48
 Met Ala Tyr Ser Glu Glu His Lys Gly Met Pro Cys Gly Phe Ile Arg
 1 5 10 15

15 CAG AAT TCC GGC AAC TCC ATT TCC TTG GAC TTT GAG CCC AGT ATA GAG 96
 Gln Asn Ser Gly Asn Ser Ile Ser Leu Asp Phe Glu Pro Ser Ile Glu
 20 25 30

20 TAC CAG TTT GTG GAG CGG TTG GAA GAG CGC TAC AAA TGT GCC TTC TGC 144
 Tyr Gln Phe Val Glu Arg Leu Glu Glu Arg Tyr Lys Cys Ala Phe Cys
 35 40 45

25 CAC TCG GTG CTT CAC AAC CCC CAC CAG ACA GGA TGT GGG CAC CGC TTC 192
 His Ser Val Leu His Asn Pro His Gln Thr Gly Cys Gly His Arg Phe
 50 55 60

30 TGC CAG CAC TGC ATC CTG TCC CTG AGA GAA TTA AAC ACA GTG CCA ATC 240
 Cys Gln His Cys Ile Leu Ser Leu Arg Glu Leu Asn Thr Val Pro Ile
 65 70 75 80

35 TGC CCT GTA GAT AAA GAG GTC ATC AAA TCT CAG GAG GTT TTT AAA GAC 288
 Cys Pro Val Asp Lys Glu Val Ile Lys Ser Gln Glu Val Phe Lys Asp
 85 90 95

40 AAT TGT TGC AAA AGA GAA GTC CTC AAC TTA TAT GTA TAT TGC AGC AAT 336
 Asn Cys Cys Lys Arg Glu Val Leu Asn Leu Tyr Val Tyr Cys Ser Asn
 100 105 110

45 GCT CCT GGA TGT AAT GCC AAG GTT ATT CTG GGC CGG TAC CAG GAT CAC 384
 Ala Pro Gly Cys Asn Ala Lys Val Ile Leu Gly Arg Tyr Gln Asp His
 115 120 125

50 CTT CAG CAG TGC TTA TTT CAA CCT GTG CAG TGT TCT AAT GAG AAG TGC 432
 Leu Gln Gln Cys Leu Phe Gln Pro Val Gln Cys Ser Asn Glu Lys Cys
 130 135 140

55 CGG GAG CCA GTC CTA CGG AAA GAC CTG AAA GAG CAT TTG AGT GCA TCC 480
 Arg Glu Pro Val Leu Arg Lys Asp Leu Lys Glu His Leu Ser Ala Ser
 145 150 155 160

TGT CAG TTT CGA AAG GAA AAA TGC CTT TAT TGC AAA AAG GAT GTG GTA 528
 Cys Gln Phe Arg Lys Glu Lys Cys Leu Tyr Cys Lys Lys Asp Val Val
 165 170 175

GTC ATC AAT CTA CAG AAT CAT GAG GAA AAC TTG TGT CCT GAA TAC CCA 576
 Val Ile Asn Leu Gln Asn His Glu Glu Asn Leu Cys Pro Glu Tyr Pro
 180 185 190

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	GTA TTT TGT CCC AAC AAT TGT GCG AAG ATT ATT CTA AAA ACT GAG GTA	624
	Val Phe Cys Pro Asn Asn Cys Ala Lys Ile Ile Leu Lys Thr Glu Val	
	195 200 205	
5	GAT GAA CAC CTG GCT GTA TGT CCT GAA GCT GAG CAA GAC TGT CCT TTT	672
	Asp Glu His Leu Ala Val Cys Pro Glu Ala Glu Gln Asp Cys Pro Phe	
	210 215 220	
10	AAG CAC TAT GGC TGT GCT GTA ACG GAT AAA CGG AGG AAC CTG CAG CAA	720
	Lys His Tyr Gly Cys Ala Val Thr Asp Lys Arg Arg Asn Leu Gln Gln	
	225 230 235 240	
15	CAT GAG CAT TCA GCC TTA CGG GAG CAC ATG CGT TTG GTT TTA GAA AAG	768
	His Glu His Ser Ala Leu Arg Glu His Met Arg Leu Val Leu Glu Lys	
	245 250 255	
	AAT GTC CAA TTA GAA GAA CAG ATT TCT GAC TTA CAC AAG AGC CTA GAA	816
	Asn Val Gln Leu Glu Glu Gln Ile Ser Asp Leu His Lys Ser Leu Glu	
	260 265 270	
20	CAG AAA GAA AGT AAA ATC CAG CAG CTA GCA GAA ACT ATA AAG AAA CTT	864
	Gln Lys Glu Ser Lys Ile Gln Gln Leu Ala Glu Thr Ile Lys Lys Leu	
	275 280 285	
25	GAA AAG GAG TTC AAG CAG TTT GCA CAG TTG TTT GGC AAA AAT GGA AGC	912
	Glu Lys Glu Phe Lys Gln Phe Ala Gln Leu Phe Gly Lys Asn Gly Ser	
	290 295 300	
30	TTC CTC CCA AAC ATC CAG GTT TTT GCC AGT CAC ATT GAC AAG TCA GCT	960
	Phe Leu Pro Asn Ile Gln Val Phe Ala Ser His Ile Asp Lys Ser Ala	
	305 310 315 320	
	TGG CTA GAA GCT CAA GTG CAT CAA TTA TTA CAA ATG GTT AAC CAG CAA	1008
	Trp Leu Glu Ala Gln Val His Gln Leu Leu Gln Met Val Asn Gln Gln	
	325 330 335	
35	CAA AAT AAA TTT GAC CTG AGA CCT TTG ATG GAA GCA GTT GAT ACA GTG	1056
	Gln Asn Lys Phe Asp Leu Arg Pro Leu Met Glu Ala Val Asp Thr Val	
	340 345 350	
40	AAA CAG AAA ATT ACC CTG CTA GAA AAC AAT GAT CAA AGA TTA GCC GTT	1104
	Lys Gln Lys Ile Thr Leu Leu Glu Asn Asn Asp Gln Arg Leu Ala Val	
	355 360 365	
45	TTA GAA GAG GAA ACT AAC AAA CAT GAT ACC CAC ATT AAT ATT CAT AAA	1152
	Leu Glu Glu Glu Thr Asn Lys His Asp Thr His Ile Asn Ile His Lys	
	370 375 380	
50	GCA CAG CTG AGT AAA AAT GAA GAG CGA TTT AAA CTG CTG GAG GGT ACT	1200
	Ala Gln Leu Ser Lys Asn Glu Glu Arg Phe Lys Leu Leu Glu Gly Thr	
	385 390 395 400	
55	TGC TAT AAT GGA AAG CTC ATT TGG AAG GTG ACA GAT TAC AAG ATG AAG	1248
	Cys Tyr Asn Gly Lys Leu Ile Trp Lys Val Thr Asp Tyr Lys Met Lys	
	405 410 415	

5 AAG AGA GAG GCG GTG GAT GGG CAC ACA GTG TCC ATC TTC AGC CAG TCC 1296
 Lys Arg Glu Ala Val Asp Gly His Thr Val Ser Ile Phe Ser Gln Ser
 420 425 430

10 TTC TAC ACC AGC CGC TGT GGC TAC CGG CTC TGT GCT AGA GCA TAC CTG 1344
 Phe Tyr Thr Ser Arg Cys Gly Tyr Arg Leu Cys Ala Arg Ala Tyr Leu
 435 440 445

15 AAT GGG GAT GGG TCA GGG AGG GGG TCA CAC CTG TCC CTA TAC TTT GTG 1392
 Asn Gly Asp Gly Ser Gly Arg Gly Ser His Leu Ser Leu Tyr Phe Val
 450 455 460

20 GTC ATG CGA GGA GAG TTT GAC TCA CTG TTG CAG TGG CCA TTC AGG CAG 1440
 Val Met Arg Gly Glu Phe Asp Ser Leu Leu Gln Trp Pro Phe Arg Gln
 465 470 475 480

25 AGG GTG ACC CTG ATG CTT CTG GAC CAG AGT GGC AAA AAG AAC ATT ATG 1488
 Arg Val Thr Leu Met Leu Leu Asp Gln Ser Gly Lys Lys Asn Ile Met
 485 490 495

30 GAG ACC TTC AAA CCT GAC CCC AAT AGC AGC AGC TTT AAA AGA CCT GAT 1536
 Glu Thr Phe Lys Pro Asp Pro Asn Ser Ser Ser Phe Lys Arg Pro Asp
 500 505 510

35 GGG GAG ATG AAC ATT GCA TCT GGC TGT CCC CGC TTT GTG GCT CAT TCT 1584
 Gly Glu Met Asn Ile Ala Ser Gly Cys Pro Arg Phe Val Ala His Ser
 515 520 525

40 GTT TTG GAG AAT GCC AAG AAC GCC TAC ATT AAA GAT GAC ACT CTG TTC 1632
 Val Leu Glu Asn Ala Lys Asn Ala Tyr Ile Lys Asp Asp Thr Leu Phe
 530 535 540

45 TTG AAA GTG GCC GTG GAC TTA ACT GAC CTG GAG GAT CTC 1671
 Leu Lys Val Ala Val Asp Leu Thr Asp Leu Glu Asp Leu
 545 550 555

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3993 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: double
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
 (B) LOCATION: 55..1725

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

	GCAGCAGCCG CGCCTGCAGA CCGGCCTCGC GGAGCCCGCG CGCCGAGCCC CACA ATG	57
	Met	
	1	
5	GCT TAT TCA GAA GAG CAT AAA GGT ATG CCC TGT GGT TTC ATC CGC CAG	105
	Ala Tyr Ser Glu Glu His Lys Gly Met Pro Cys Gly Phe Ile Arg Gln	
	5 10 15	
10	AAT TCC GGC AAC TCC ATT TCC TTG GAC TTT GAG CCC AGT ATA GAG TAC	153
	Asn Ser Gly Asn Ser Ile Ser Leu Asp Phe Glu Pro Ser Ile Glu Tyr	
	20 25 30	
15	CAG TTT GTG GAG CGG TTG GAA GAG CGC TAC AAA TGT GCC TTC TGC CAC	201
	Gln Phe Val Glu Arg Leu Glu Glu Arg Tyr Lys Cys Ala Phe Cys His	
	35 40 45	
20	TCG GTG CTT CAC AAC CCC CAC CAG ACA GGA TGT GGG CAC CGC TTC TGC	249
	Ser Val Leu His Asn Pro His Gln Thr Gly Cys Gly His Arg Phe Cys	
	50 55 60 65	
25	CAG CAC TGC ATC CTG TCC CTG AGA GAA TTA AAC ACA GTG CCA ATC TGC	297
	Gln His Cys Ile Leu Ser Leu Arg Glu Leu Asn Thr Val Pro Ile Cys	
	70 75 80	
30	CCT GTA GAT AAA GAG GTC ATC AAA TCT CAG GAG GTT TTT AAA GAC AAT	345
	Pro Val Asp Lys Glu Val Ile Lys Ser Gln Glu Val Phe Lys Asp Asn	
	85 90 95	
35	TGT TGC AAA AGA GAA GTC CTC AAC TTA TAT GTA TAT TGC AGC AAT GCT	393
	Cys Cys Lys Arg Glu Val Leu Asn Leu Tyr Val Tyr Cys Ser Asn Ala	
	100 105 110	
40	CCT GGA TGT AAT GCC AAG GTT ATT CTG GGC CGG TAC CAG GAT CAC CTT	441
	Pro Gly Cys Asn Ala Lys Val Ile Leu Gly Arg Tyr Gln Asp His Leu	
	115 120 125	
45	CAG CAG TGC TTA TTT CAA CCT GTG CAG TGT TCT AAT GAG AAG TGC CGG	489
	Gln Gln Cys Leu Phe Gln Pro Val Gln Cys Ser Asn Glu Lys Cys Arg	
	130 135 140 145	
50	GAG CCA GTC CTA CGG AAA GAC CTG AAA GAG CAT TTG AGT GCA TCC TGT	537
	Glu Pro Val Leu Arg Lys Asp Leu Lys Glu His Leu Ser Ala Ser Cys	
	150 155 160	
55	CAG TTT CGA AAG GAA AAA TGC CTT TAT TGC AAA AAG GAT GTG GTA GTC	585
	Gln Phe Arg Lys Glu Lys Cys Leu Tyr Cys Lys Lys Asp Val Val Val	
	165 170 175	
60	ATC AAT CTA CAG AAT CAT GAG GAA AAC TTG TGT CCT GAA TAC CCA GTA	633
	Ile Asn Leu Gln Asn His Glu Glu Asn Leu Cys Pro Glu Tyr Pro Val	
	180 185 190	
65	TTT TGT CCC AAC AAT TGT GCG AAG ATT ATT CTA AAA ACT GAG GTA GAT	681
	Phe Cys Pro Asn Asn Cys Ala Lys Ile Ile Leu Lys Thr Glu Val Asp	
	195 200 205	

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GAA CAC CTG GCT GTA TGT CCT GAA GCT GAG CAA GAC TGT CCT TTT AAG	729
Glu His Leu Ala Val Cys Pro Glu Ala Glu Gln Asp Cys Pro Phe Lys	
210 215 220 225	
CAC TAT GGC TGT GCT GTA ACG GAT AAA CGG AGG AAC CTG CAG CAA CAT	777
His Tyr Gly Cys Ala Val Thr Asp Lys Arg Arg Asn Leu Gln Gln His	
230 235 240	
GAG CAT TCA GCC TTA CGG GAG CAC ATG CGT TTG GTT TTA GAA AAG AAT	825
Glu His Ser Ala Leu Arg Glu His Met Arg Leu Val Leu Glu Lys Asn	
245 250 255	
GTC CAA TTA GAA GAA CAG ATT TCT GAC TTA CAC AAG AGC CTA GAA CAG	873
Val Gln Leu Glu Glu Gln Ile Ser Asp Leu His Lys Ser Leu Glu Gln	
260 265 270	
AAA GAA AGT AAA ATC CAG CAG CTA GCA GAA ACT ATA AAG AAA CTT GAA	921
Lys Glu Ser Lys Ile Gln Gln Leu Ala Glu Thr Ile Lys Lys Leu Glu	
275 280 285	
AAG GAG TTC AAG CAG TTT GCA CAG TTG TTT GGC AAA AAT GGA AGC TTC	969
Lys Glu Phe Lys Gln Phe Ala Gln Leu Phe Gly Lys Asn Gly Ser Phe	
290 295 300 305	
CTC CCA AAC ATC CAG GTT TTT GCC AGT CAC ATT GAC AAG TCA GCT TGG	1017
Leu Pro Asn Ile Gln Val Phe Ala Ser His Ile Asp Lys Ser Ala Trp	
310 315 320	
CTA GAA GCT CAA GTG CAT CAA TTA TTA CAA ATG GTT AAC CAG CAA CAA	1065
Leu Glu Ala Gln Val His Gln Leu Leu Gln Met Val Asn Gln Gln Gln	
325 330 335	
AAT AAA TTT GAC CTG AGA CCT TTG ATG GAA GCA GTT GAT ACA GTG AAA	1113
Asn Lys Phe Asp Leu Arg Pro Leu Met Glu Ala Val Asp Thr Val Lys	
340 345 350	
CAG AAA ATT ACC CTG CTA GAA AAC AAT GAT CAA AGA TTA GCC GTT TTA	1161
Gln Lys Ile Thr Leu Leu Glu Asn Asn Asp Gln Arg Leu Ala Val Leu	
355 360 365	
GAA GAG GAA ACT AAC AAA CAT GAT ACC CAC ATT AAT ATT CAT AAA GCA	1209
Glu Glu Glu Thr Asn Lys His Asp Thr His Ile Asn Ile His Lys Ala	
370 375 380 385	
CAG CTG AGT AAA AAT GAA GAG CGA TTT AAA CTG CTG GAG GGT ACT TGC	1257
Gln Leu Ser Lys Asn Glu Glu Arg Phe Lys Leu Leu Glu Gly Thr Cys	
390 395 400	
TAT AAT GGA AAG CTC ATT TGG AAG GTG ACA GAT TAC AAG ATG AAG AAG	1305
Tyr Asn Gly Lys Leu Ile Trp Lys Val Thr Asp Tyr Lys Met Lys Lys	
405 410 415	
AGA GAG GCG GTG GAT GGG CAC ACA GTG TCC ATC TTC AGC CAG TCC TTC	1353
Arg Glu Ala Val Asp Gly His Thr Val Ser Ile Phe Ser Gln Ser Phe	
420 425 430	

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5
TAC ACC AGC CGC TGT GGC TAC CGG CTC TGT GCT AGA GCA TAC CTG AAT 1401
Tyr Thr Ser Arg Cys Gly Tyr Arg Leu Cys Ala Arg Ala Tyr Leu Asn
435 440 445

10
GGG GAT GGG TCA GGG AGG GGG TCA CAC CTG TCC CTA TAC TTT GTG GTC 1449
Gly Asp Gly Ser Gly Arg Gly Ser His Leu Ser Leu Tyr Phe Val Val
450 455 460 465

15
ATG CGA GGA GAG TTT GAC TCA CTG TTG CAG TGG CCA TTC AGG CAG AGG 1497
Met Arg Gly Glu Phe Asp Ser Leu Leu Gln Trp Pro Phe Arg Gln Arg
470 475 480

20
GTG ACC CTG ATG CTT CTG GAC CAG AGT GGC AAA AAG AAC ATT ATG GAG 1545
Val Thr Leu Met Leu Leu Asp Gln Ser Gly Lys Lys Asn Ile Met Glu
485 490 495

25
ACC TTC AAA CCT GAC CCC AAT AGC AGC AGC TTT AAA AGA CCT GAT GGG 1593
Thr Phe Lys Pro Asp Pro Asn Ser Ser Ser Phe Lys Arg Pro Asp Gly
500 505 510

30
GAG ATG AAC ATT GCA TCT GGC TGT CCC CGC TTT GTG GCT CAT TCT GTT 1641
Glu Met Asn Ile Ala Ser Gly Cys Pro Arg Phe Val Ala His Ser Val
515 520 525

35
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Lys Val Ala Val Asp Leu Thr Asp Leu Glu Asp Leu
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(2) INFORMATION FOR SEQ ID NO: 7:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 34 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
 (A) DESCRIPTION: /desc = "primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

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(2) INFORMATION FOR SEQ ID NO: 8:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 32 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
 (A) DESCRIPTION: /desc = "primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

GCGTCGACTC AAAAGGTCAG CAAGCAGCCA TC

(2) INFORMATION FOR SEQ ID NO: 9:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 33 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: other nucleic acid
 (A) DESCRIPTION: /desc = "primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

CTCCTCGAGA TGGAGTCGAG TAAAAAGATG GAC

(2) INFORMATION FOR SEQ ID NO: 10:

- (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:
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(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:
GCAGCAGCCG CGCCTGCAGA CCGGC 25

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "primer"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:
ATCCAGGAGC ATTGCTGCAA TATAC 25

55 Claims

1. TRAF5 protein associating with the intracellular domain of CD40.

2. A polypeptide comprising at least one of the polypeptides having an amino acid sequence shown as No.45-84, No.110-249, No.251-403 or No.404-558 of the SEQ ID No.1 in the Sequence Listing.
3. A polypeptide comprising at least one of the polypeptides having an amino acid sequence shown as No.45-84, No.110-249, No.251-403 or No.404-557 of the SEQ ID No.4 of the Sequence Listing.
4. A polypeptide comprising the polypeptide of the SEQ ID No.1 in the Sequence Listing.
5. A polypeptide comprising the polypeptide of the SEQ ID No.4 in the Sequence Listing.
6. A polypeptide consisting of the polypeptide of the SEQ ID No.1 in the Sequence Listing or any part thereof.
7. A polypeptide consisting of the polypeptide of the SEQ ID No.4 in the Sequence Listing or any part thereof.
8. A DNA comprising the base sequence encoding the polypeptide comprising at least one of the polypeptides having an amino acid sequence shown as No.45-84, No.110-249, No.251-403 or No.404-558 of the SEQ ID No.1 in the Sequence Listing.
9. A DNA comprising the base sequence encoding the polypeptide comprising at least one of the polypeptides having an amino acid sequence shown as No.45-84, No.110-249, No.251-403 or No.404-557 of the SEQ ID No.4 of the Sequence Listing.
10. A DNA comprising the base sequence encoding the polypeptide of Claim 6.
11. A DNA comprising the base sequence encoding the polypeptide of Claim 7.
12. A DNA comprising the base sequence of the SEQ ID No.2 in the sequence Listing or any part thereof.
13. A DNA comprising the base sequence of the SEQ ID No.5 in the Sequence Listing or any part thereof.
14. An antisense oligonucleotide and its derivatives for the DNA of Claim 8, 10 or 12.
15. An antisense oligonucleotide and its derivatives for the DNA of Claim 9, 11 or 13.
16. An antibody which recognizes the TRAF5 of Claim 1.
17. An antibody which recognizes the polypeptide of Claim 2, 4 or 6.
18. An antibody which recognizes the polypeptide of Claim 3, 5 or 7.
19. An antibody of Claim 16, 17 or 18, which inhibits CD40-mediated signal transduction.
20. A monoclonal antibody of Claim 16, 17, 18 or 19.
21. A vector comprising the DNA of Claim 8, 10 or 12.
22. A vector comprising the DNA of Claim 9, 11 or 13.
23. A transformant which is transformed by the vector of Claim 21.
24. A transformant which is transformed by the vector of Claim 22.
25. A method for the production of TRAF5 or the polypeptide, comprising culturing the transformant of Claim 23.
26. A method for the production of TRAF5 or the polypeptide, comprising culturing the transformant of Claim 24.
27. A method for the screening of the substance which binds to TRAF5 protein of Claim 1, or the polypeptide of one of Claim 2 to 7, or regulates the activity or the expression of TRAF5 protein of Claim 1, or the polypeptide of one of

Claim 2 to 7, using said TRAF5 protein, said polypeptide, or the antibody of one of Claim 16 to 18.

28. The substances obtained by the screening method of Claim 27, which binds to TRAF5 protein of Claim 1 or the polypeptide of one of Claim 2 to 7, or regulates their activity or expression.

29. A medical composition used for the treatment of immune diseases, comprising the TRAF5 protein of Claim 1 or the polypeptide of one of Claim 2 to 7 as an effective ingredient.

30. A medical composition used for the treatment of allergy, comprising the TRAF5 protein of Claim 1 or the polypeptide of one of Claim 2 to 7 as an effective ingredient.

31. A medical composition with cell growth-inhibiting activity, comprising the TRAF5 protein of Claim 1 or the polypeptide of one of Claim 2 to 7 as an effective ingredient.

32. A medical composition used for the treatment of immune diseases, comprising the antisense oligonucleotide of Claim 14 or 15 or its derivatives as an effective ingredient.

33. A medical composition used for the treatment of allergy, comprising the antisense oligonucleotide of Claim 14 or 15 or its derivatives as an effective ingredient.

34. A medical composition with cell growth-inhibiting activity, comprising the antisense oligonucleotide of Claim 14 or 15 or its derivatives as an effective ingredient.

35. A medical composition used for the treatment of immune diseases, comprising the antibody of one of Claim 16 to 20 as an effective ingredient.

36. A medical composition used for the treatment of allergy, comprising the antibody of one of Claim 16 to 20 as an effective ingredient.

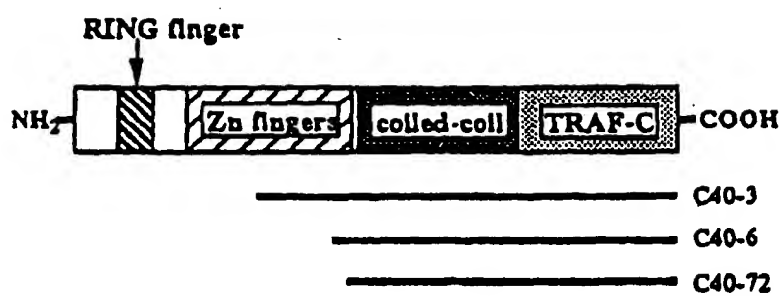
37. A medical composition with cell growth-inhibiting activity, comprising the antibody of one of Claim 16 to 20 as an effective ingredient.

38. A medical composition used for the treatment of immune diseases, comprising the substance of Claim 28 as an effective ingredient.

39. A medical composition used for the treatment of allergy, comprising the substance of Claim 28 as an effective ingredient.

40. A medical composition with cell growth-inhibiting activity, comprising the substance of Claim 28 as an effective ingredient.

Fig 1



[illegible]

Fig 3

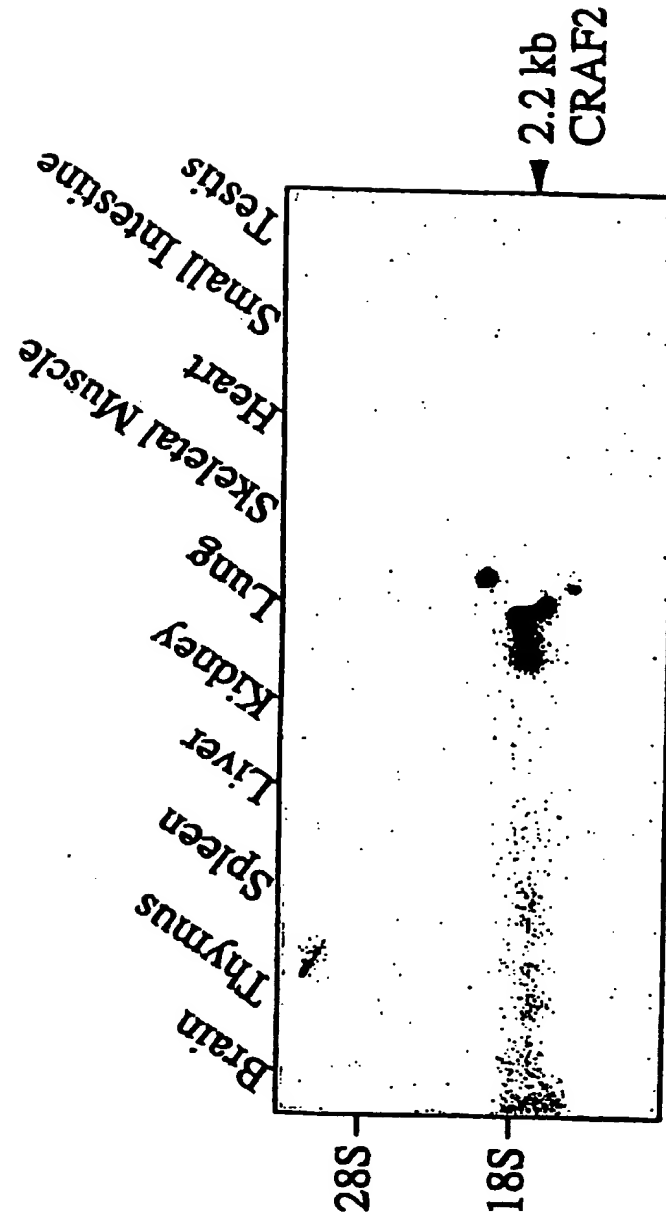


Fig 4

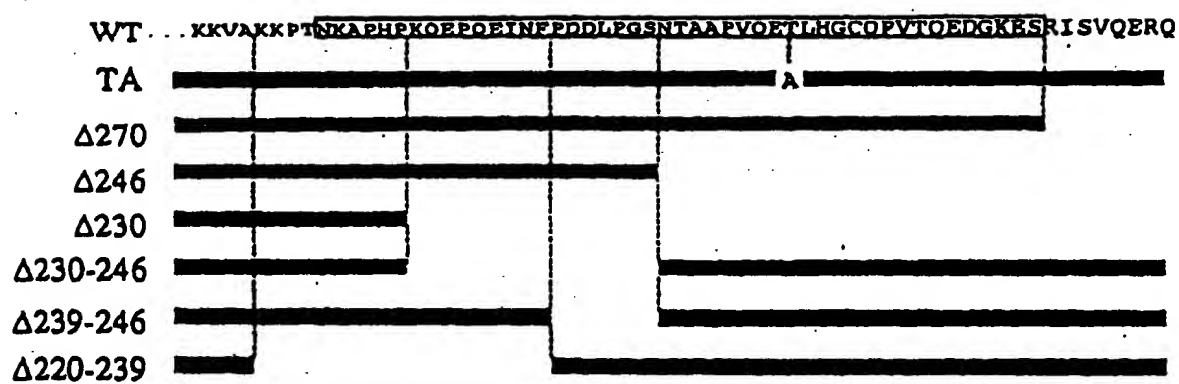


Fig 5

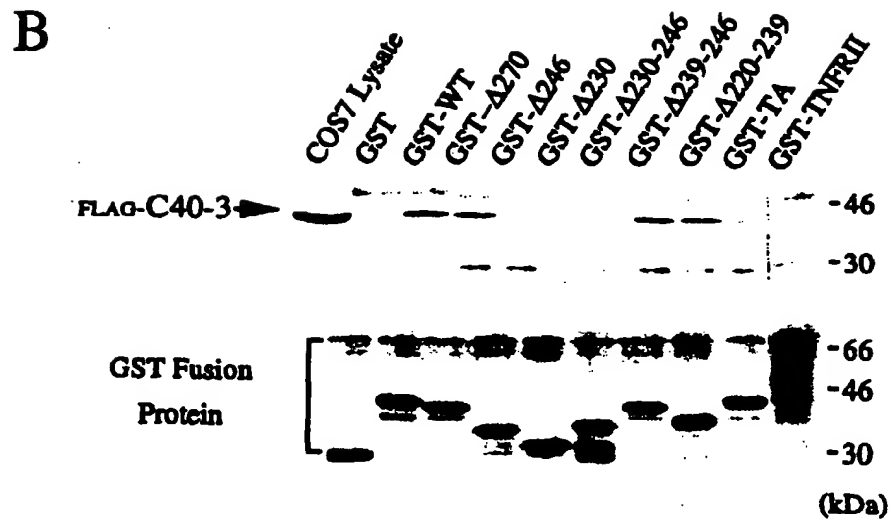


Fig 6

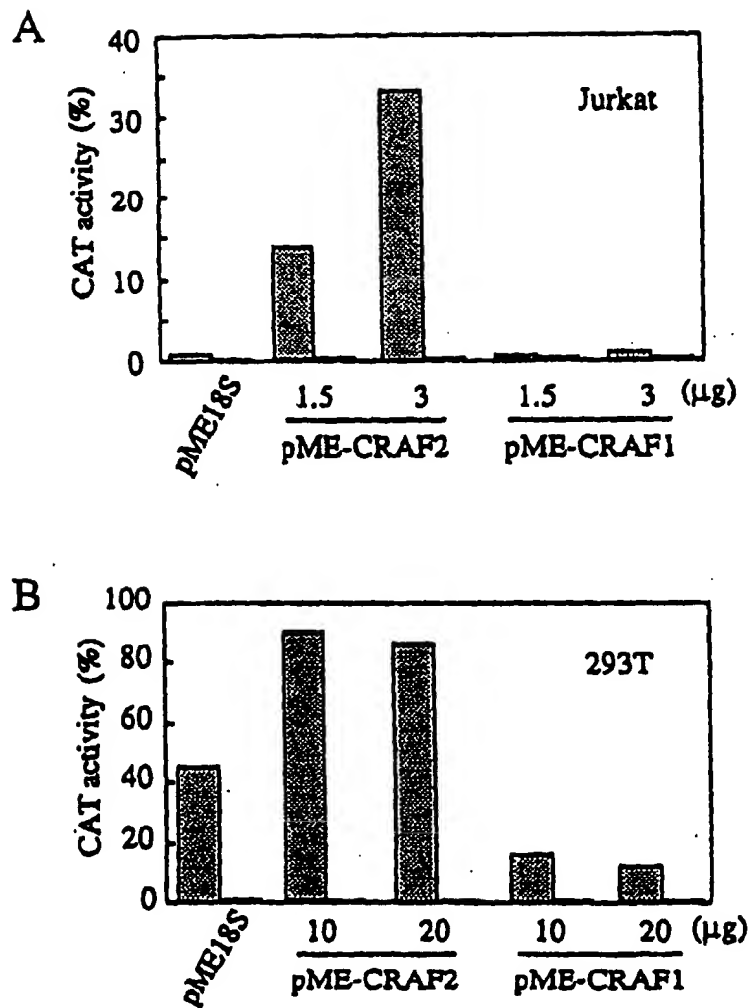


Fig 7

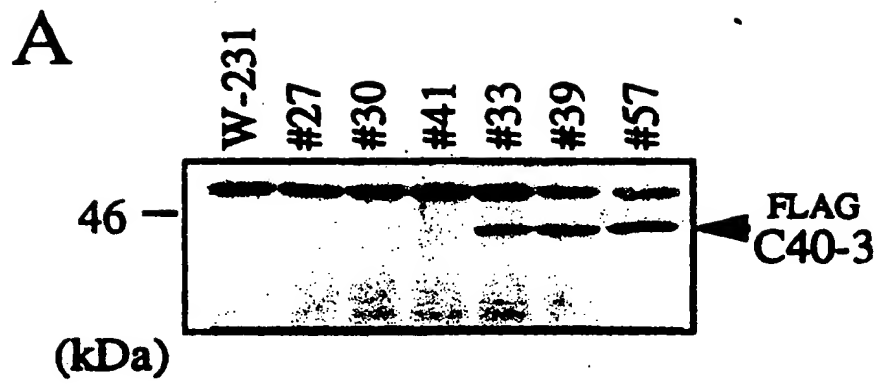


Fig 8

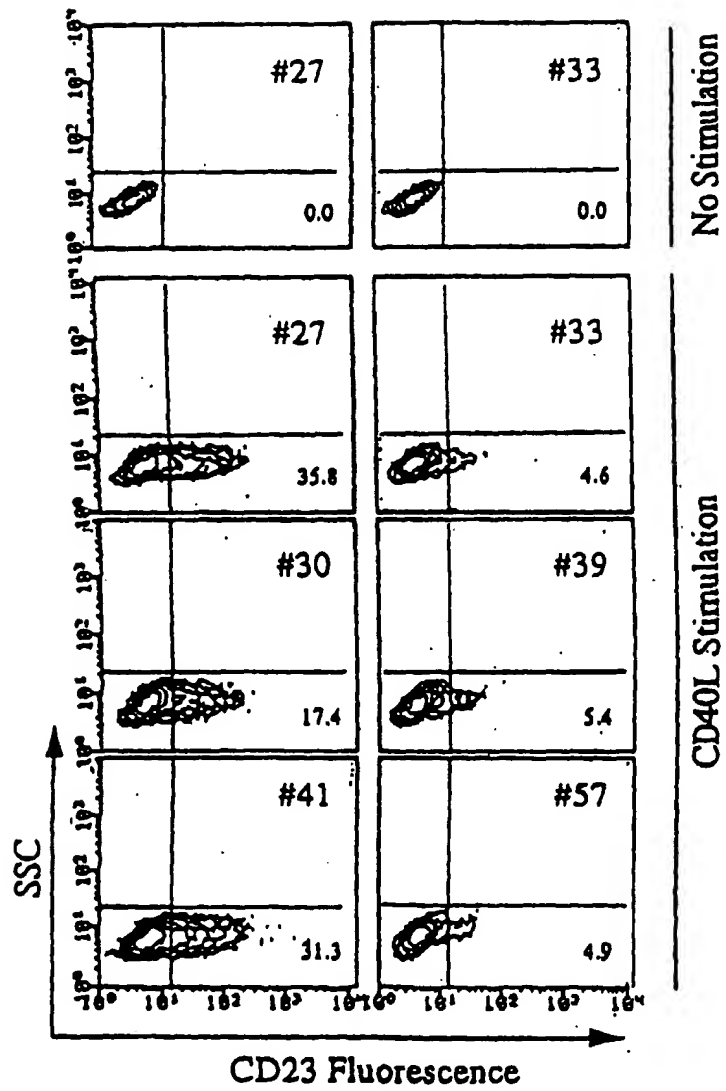


Fig 9

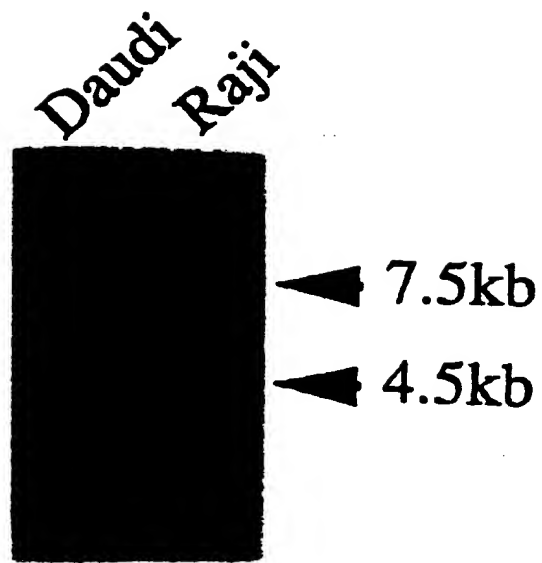
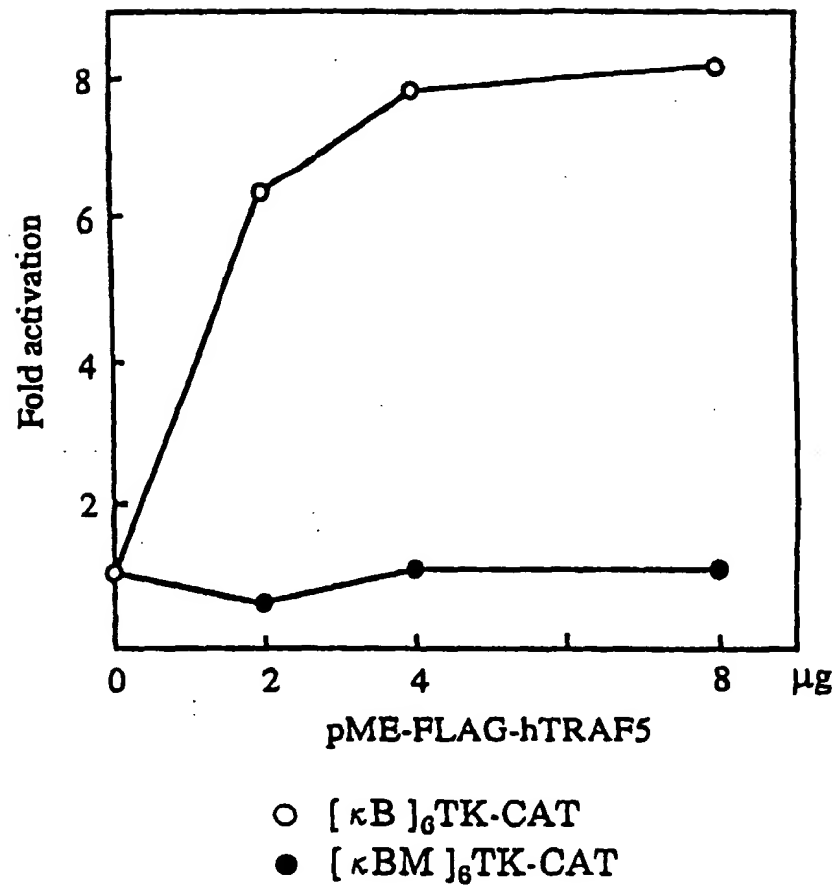


Fig 10



INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP97/01236

A. CLASSIFICATION OF SUBJECT MATTER Int. Cl ⁶ C12N15/12, C12P21/02, C12N1/21, C12N5/10, G01N33/53, C07K14/435, C07K16/18, A61K38/17, A61K39/395 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int. Cl ⁶ C12N15/12, C12P21/02, C12N1/21, C12N5/10, G01N33/53, C07K14/435, C07K16/18, A61K38/17, A61K39/395 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WPI, WPI/L, BIOSIS PREVIEWS, CAS ONLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	Hiroyasu, N. et al. "TRAF5, an Activator of NF-KB and Putative Signal Transducer for the Lymphotoxin-beta Receptor" J. Biol.Chem. (1996, Jun.), Vol. 271, No. 25, p. 14661-14664	1 - 40
PX	Takaomi I. et al. "TRAF5, a novel tumor necrosis factor receptor-associated factor family protein, mediates CD40 signaling" Proc. Natl. Acad. Sci. USA (1996, Sep.), Vol. 93, p. 9437-9442	1 - 40
PX	Inoue T. et al. "TRAF5 and TRAF6 mediate CD40 signaling" J. Allergy Clin. Immunol. (1997, Jan.) Vol. 99 1pt2 p.S470	1 - 40
A	Takaaki S. et al. "A novel member of the TRAF family of putative signal transducing proteins binds to the cytosolic domain of CD40" FEBS letters (1995) Vol. 358, p. 113-118	1 - 40
A	Genhong C. et al. "Involvement of CRAF1, a	1 - 40
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search July 1, 1997 (01. 07. 97)		Date of mailing of the international search report July 8, 1997 (08. 07. 97)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.		Authorized officer Telephone No.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP97/01236

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Relative of TRAF, in CD40 Signaling" Science (1995) Vol. 267, p. 1494-1498	
A	Hong M.H. et al. "A Novel RING Finger Protein Interacts with the Cytoplasmic Domain of CD40" J. Biol. Chem. (1994) Vol. 269, No. 48, p. 30069-30072	1 - 40
PA	Takaomi I. et al. "Identificaiton of TRAF6, a Novel Tumor Necrosis Factor Receptor-Associated Factor Protein That Mediates Signaling from an Amino-terminal Domain of the CD40 Cytoplasmic Region" J. Biol. Chem. (1996, Nov.) Vol. 271, No. 46, p. 28745-28748	1 - 40

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